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BULLETIN OF
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ELECTRICAL RESPONSES TO TWO CLICKS: A SIMPLE STATISTICAL INTERPRETATION*

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A probability model for the amplitude of the first neural component, N_1, of the click response has been developed on the assumption that N_1 is the summated effect of practically simultaneous firing from large numbers of independent neural units. Equations derived from the model predict the course of recovery for the response to the second of two clicks. A mathematical relation is shown between the two-click situation and the intensity growth curve for the first neural component of the response to a single click. This permits indirect reconstruction of the function relating amplitude of N_1 to stimulus intensity. Experiments with pairs of clicks indicate that a normal probability integral provides a satisfactory fit. Thus the entire intensity function of N_1 is capable of specification in terms of two statistical parameters, the mean and the standard deviation of the normal integral. Factors that affect the click response are presumed to act upon these parameters.

When a sharp click is delivered to the ear of an anesthetized cat, a characteristic electrical response can be recorded from an electrode in contact with the round window. The response consists chiefly of two kinds of activity: (1) a so-called microphonic potential, whose initial deflection is positive or negative, depending upon the polarity of the click, and (2) neural potentials, which are always negative. There are several ways of differentiating the microphonic from the neural portions of the response. For our purposes, the most significant of these is the fact that over a wide range of intensities the amplitude of the microphonic is linear with the stimulus. Neural components, on the other hand, behave in a rather complex fashion with changes in stimulus intensity.

*This research was carried out under Contract N5ori-76 between Harvard University and the Office of Naval Research, U. S. Navy (Project Nr142-201, Report PNR-107). Reproduction for any purpose by the U. S. Government is permitted.

Of particular interest in connection with this paper is the earliest neural component, which we shall call N_1. It is the first and largest neural potential recordable at the round window with a peak of excitation occurring approximately 1 millisecond after the acoustic stimulus reaches the eardrum. Presumably it represents the response of neural structures near the auditory end organs (Davis et al., 1950). Whatever its origin, this earliest neural event is still close to the measurable physical stimulus and probably constitutes the primary neural input to the auditory nervous system. Its behavior is clearly related to such well-known auditory phenomena as masking and fatigue (Rosenblith, 1950). Thus considerable interest can be invested in studying the growth of the first neural component as a function of stimulus magnitude.

Direct measurements of N_1, however, are somewhat troublesome, for the microphonic and neural components are separated in time for weak clicks only. They exhibit severe interaction as the click stimulus gets louder. Amplitude measurements of components of the round window response are thus likely to be considerably biased. At the same time experimental methods for manipulating the microphonic independently of the neural portions of the response are still in an incomplete stage of development (Kahana et al., 1950). In the face of such difficulties, we have attempted to reconstruct the function relating amplitude of N_1 to stimulus intensity through the application of a simple probability model.

To develop the concepts underlying the model, the click response must be examined in a somewhat different situation. If two clicks are presented to the ear, separated by a time interval of about 100 milliseconds or less, the neural response to the second click is depressed, i.e., the ratio of the neural amplitude of the second click response to the resting (normal) amplitude of the same response is less than 1, depending upon the time separation of the clicks.* Our experiments indicate that the amount of depression is governed by three obvious factors: the intensity of the first click, the time interval between clicks, and the intensity of the second click.

*The microphonic component of the response to the second click remains unaffected over the intensity range we have used. If the two clicks are separated by time intervals of less than 2 milliseconds, the two responses cannot easily be resolved and measurements of microphonics and neurals may become "confounded." For the time course of the recovery functions for the amplitude of the neural response to the second click see M. R. Rosenzweig and W. A. Rosenblith (1950).

We have observed too that the relative amplitude of N_1 in the response to the second click is not zero even at 2 milliseconds.* Finally our results indicate that component N_1 of the second click does not become supernormal.

We assume that the first neural part of the click response is the summated effect of firing from large numbers of neural units. If all neural units contribute nearly the same average voltage to the total response, then

$$A_{N_1} = \sum_i R_i = n\bar{R}, \tag{1}$$

where A_{N_1} is the peak-to-peak amplitude of N_1, R_i is the voltage contributed by the ith neural unit; n is the number of neural units responding simultaneously, and $\bar{R}$ is the average voltage (at the location of the electrode). Thus it follows that the amplitude of the click response at the round window is proportional to the number of units responding. This assumption we shall discuss shortly.

Suppose that, corresponding to any given stimulus intensity, there is a fixed probability that a neural unit will respond in normal conditions. To facilitate discussion we shall label this and certain other probabilities as follows:

$p(I)$ = the (resting) probability of response of a neural unit to the first click which is at intensity I.

$p(J)$ = the (resting) probability of response to the second click which is at intensity J.

$p^*(t)$ = a probability operator representing the recovery of a neural unit that has fired. It is a function of the time since firing and of the intensity of the second click.

P_{12} = the probability that a neural unit fires twice to successive click stimuli.

P_{02} = the probability that a neural unit fails to fire to the first click but fires in response to the second.

All possible outcomes in the two-click situation may then be represented as follows:

*Listening to two clicks separated by time intervals of less than 2 milliseconds confirms this statement to the extent that two clicks are perceived as "more" (i.e. louder, fuzzier, more spread out) than one.

$$P_{12} = p(I) \cdot p^*(t) \cdot p(J), \tag{2}$$

$$P_{02} = [1 - p(I)] \cdot p(J), \tag{3}$$

$$P_{10} = p(I) \cdot [1 - p^*(t) \cdot p(J)], \tag{4}$$

$$P_{00} = [1 - p(I)][1 - p(J)]. \tag{5}$$

The probability, P_2, that a neural unit fires in response to the second click is the sum of P_{12} and P_{02} above:

$$P_2 = p(I) \cdot p^*(t) \cdot p(J) + [1 - p(I)] \cdot p(J). \tag{6}$$

If we postulate that $p^*(t)$ approaches zero as t, the time separation of the two clicks, approaches zero (i.e., in the absolute refractory period of any neural unit having fired in response to the first click), then

$$\lim_{t \to 0} P_2 = [1 - p(I)] \cdot p(J).$$

The relative amplitude of N_1 in the second click response is not zero unless the first click is of maximum intensity. Also we note that when $p^*(t)$ reaches 1 at some time t', dependent upon the intensity of the second click, then:

$$\lim_{t \geq t'} P_2 = p(J).$$

Let us define RA as the relative amplitude of N_1, i.e., as the ratio of the amplitude of N_1 in the second click response to its resting amplitude. Thus we have on the average:

$$RA = \frac{N \cdot P_2}{N \cdot p(J)}, \tag{7}$$

where N is the total number of neural units capable of responding. By substituting (6) into (7) we find

$$RA = 1 - p(I) \cdot [1 - p^*(t)]. \tag{8}$$

If we fix the intensity of the second click and the time separation between clicks, it is clear that RA is simply a linear function of the intensity of the first click.

The experiment outlined above, in which a conditioning click precedes a weak test click, permits us to reconstruct the curve relating amplitude of N_1 to stimulus intensity. Figure 1 presents the actual results of such an experiment. The experimental points are

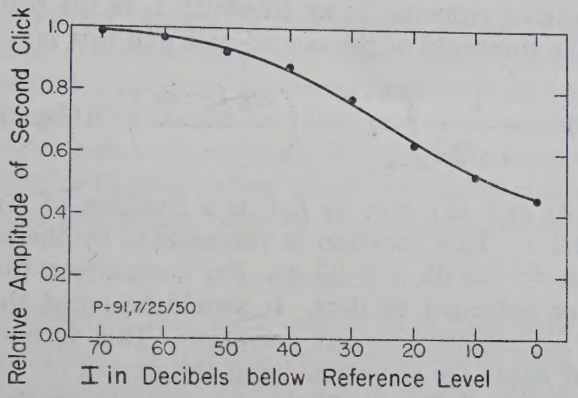

FIGURE 1. Effect of preceding click ($t = 9.1$ milliseconds) upon the amplitude of N_1 in the response to the second click. The abscissa gives the intensity of the first click. The second click is constant at —20 db. The curve is fitted by $RA = 1 - c \cdot p(I)$ in which constants are chosen as follows: $c = .60$, $m = -25$ db, $\sigma = 20$ db.

mean values of not less than 15 and not more than 25 observations of individual click responses from a single cat. To fit a theoretical curve to the data of Figure 1 we have attempted to analyze $p(I)$ in a familiar way. It is well known that thresholds of individual neurons are not constant. There is indeed reasonable ground for holding that the determinants of an instantaneous threshold are sufficiently complex to constitute the observed threshold of a neuron as a normal variable. The work of C. R. Pecher (1939) on sciatic nerve fibers in the frog confirms this and indicates that thresholds of adjacent neurons are independent. It is surely no accident that the response amplitude of the whole sciatic nerve as a function of stimulus intensity can be represented quite well by a normal probability integral (von Brücke et al., 1941). W. J. Crozier (1940) has argued at some length that variation of neural thresholds is of primary importance for understanding visual intensity phenomena. Indeed it was Crozier who pointed out explicitly that relations between stimulus intensity and neural response attributable to variation of neural thresholds ought to be found in other sense modalities.

The auditory neural unit, then, is assumed to have a threshold intensity I_T which varies at random in normal fashion. If, during the instant of stimulation, the stimulus intensity is at or above the threshold, (i.e., for all $I \geqslant I_T$) the neural unit fires. If it is below the threshold, the unit does not fire. Our assumptions indicate that

the probability of response to an intensity I_0 is the probability that I_0 is above the threshold of the neural unit and this is:

$$p(I) = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{\log I_0} e^{-\frac{1}{2}\left(\frac{\log I - m}{\sigma}\right)^2} d(\log I). \qquad (9)$$

Equations (8) and (9) give us RA as a function of I and of parameters m and σ. This function is represented by the curve of Figure 1 with $m = -25$ db, $\sigma = 20$ db. For comparison the experimental points are indicated by dots. It should be noted that $p(I)$ is a function of log intensity in our definition. This formulation is imposed by our data. On the other hand the curves of Pecher (1938) and E. T. von Brücke et al. (1941) appear to be on linear intensity scales. We are prepared to offer no simple explanation of the discrepancy, other than to point out that our measures of intensity refer to the acoustic click and not to proximal electrical stimulation. A number of alternative hypotheses may be offered to account for the log transformation. We see no reason for committing ourselves to any one at the present time.

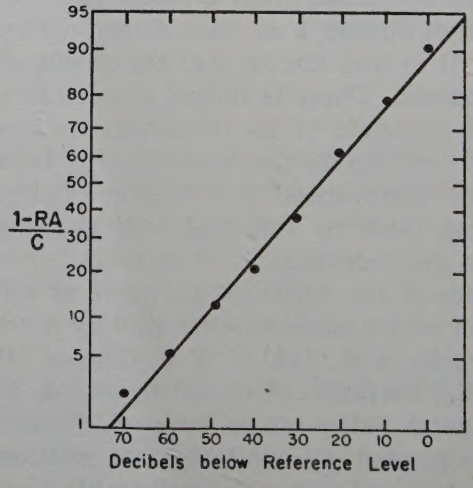

FIGURE 2. The reconstructed intensity growth function of N_1. The ordinate is a probability grid on which a normal integral is linear. The experimental points are taken from Figure 1. Similar functions have been obtained for different intensities of the second click from this same animal, as well as from other experimental animals.

Figure 2 shows $p(I)$ reconstructed from the curve of relative amplitude in Figure 1. The points are plotted on a probability grid

on which the normal integral is rectilinear. In all it appears that our assumptions are reasonably validated by our results. We have fitted the data of Figure 2 to the intensity growth curve of the first neural component. The results are as expected (Rosenblith and McGill, unpublished data); N_1 follows the theoretical curve until the microphonic begins to grow, after which the neural component oscillates around the theoretical value as intensity increases.

Discussion

We have assumed that each neural unit fires with nearly the same average voltage. It is quite unlikely, however, that the magnitude of the response emitted by any single neural unit is constant or that any two units contribute exactly the same amount to the total response. We can, on the other hand, interpret the response magnitude of a neural unit in the same way as we have dealt with its excitability, i.e., by stating the probability of a response of magnitude R_0, namely $p(R_0)$. The mean value of response magnitude will then be, assuming a finite expectation:

$$\mu_R = E(R_j). \tag{10}$$

If the probability of firing is statistically independent of the probability of a given response magnitude, then the expected magnitude of the total response in a population of N neural units is $N \cdot p(I) \cdot \mu_R$. Independence here implies an all-or-none law for neural activity, which is somewhat unusual in comparison with the common formulation, but it is nevertheless effective. Actually an all-or-none law of sorts has been implicit in our entire development. The refractory period operator $p^*(t)$ has been described as a function of two variables: time separation of the two clicks and intensity of the second click.* In the two-click problem we concern ourselves not with the stimulus intensity that fires a single neural unit, but only with the fact that it fires. We cannot, however, neglect the intensity of the second stimulus. Our experiments show clearly that a given stage of recovery of the second click response is reached much more rapidly as the intensity of the second click increases.

The fact that component N_1 of the click response does not become supernormal when paired with a preceding click permits us to treat $p^*(t)$ as a simple recovery probability, or geometrically as

*The term refractory period is employed here in a generic sense. For a discussion of refractoriness, depression, fatigue, and their interrelations, see R. Lorente de Nó (1947, p. 367).

a probability plane with time and intensity of the second click as coordinates. Undoubtedly the most general formulation of $p^*(t)$ is in terms of a transform on the parameters (m and σ) of the second click response. Nevertheless, we have chosen to work with the recovery probability in order to preserve the simplicity inherent in responses to pairs of clicks. In the present paper we have not been concerned with the mathematical expression for the $p^*(t)$ operator (which has been absorbed into the constant c). The operator is, however, amenable to direct experimental analysis and will be dealt with empirically in a subsequent paper.

We do not require that each neural unit have the same mean threshold intensity or the same sigma. As a matter of fact we can conceive K classes of neural units with different threshold distributions. Each class might contain an appropriate number, n_k, of neural units having an average response magnitude, μ_{Rk}. In this case the number of elements and the average response magnitude constitute weighting factors for each threshold distribution. We rely upon a well-known statistical theorem which states that a linear combination of normal variables is itself normally distributed, to guarantee that the average of classes of neural units behaves as our experiments seem to indicate.

So far we have dealt with a single problem: the amplitude of the first neural component of the round window response to clicks. Thus, we have considered only one aspect of a complex response, disregarding in our present formulation changes in latency, temporal dispersion, and behavior of other neural components. We feel rather confident that the present model does not contain features that would prevent us from extending our predictions to these other dimensions of the response. It is, as a matter of fact, not too hard to see how the flexibility of the $p^*(t)$ operator might permit us to investigate such phenomena as fatigue, masking, or recruitment, or to account for the effect of certain physical variables such as temperature upon the click response. There are many ways in which we can manipulate the experimental situation to get at the $p^*(t)$ operator and its parameters—and this, after all, is at least one of the functions of a mathematical model in electrophysiological research.

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A SUGGESTION FOR A MATHEMATICAL APPROACH TO THE PROBLEM OF THE EFFECT OF CLIMATIC FACTORS ON HEALTH

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It is suggested that the effect of sudden temperature changes upon the organism may be due to the variation of two factors, whose rates of changes are functions of the temperature. It is assumed that the variations of the two factors follow differential equations which are formally identical with those of the two-factor theory of excitation, and in which the temperature formally plays the role of the stimulus. By proper choice of the parameters the two factors are made equal for any constant temperature. Assuming that the greater the absolute value of the difference of the two factors, the greater is the instability of the organism, and the greater is its susceptibility to disease, relations between the suddenness of temperature changes and disease incidence are derived. The incidence of weather-affected disease for a given period of time is found to be a linear function of the mean hourly temperature variation during that period, a relation which can be in principle verified.

Paraphrasing the well known remark of Mark Twain we may say that a great deal has been written about effects of climate and weather on health, but very little, if any, scientific study has been undertaken. The most prolific writer on the subject in this country was undoubtedly the late William F. Petersen. The several huge volumes of his *The Patient and The Weather* (Petersen, 1936–38) contain an enormous number of diagrams and charts, which, unfortunately, could not convince a scientist. While they purport to show a close parallelism between climatic variations and variations of health, not a single correlation coefficient is computed, and no quantitative treatment of the data is given. In his *Man, Weather, Sun* (1947) Petersen does give correlation coefficients between climatic changes and some pathological changes, but a recomputation of some of the coefficients, taken at random from the data given in text, gives quite different values than those claimed by Petersen.

A much more modest approach to the problem was made by Manuel Morales and Eugenia Tarver (1948), who observed the in-

cidence of some diseases among the crew of the battleship *Washington* as the ship traveled through different climatic environments. The results show a very clear increase in incidence of respiratory disease associated with sudden drops in temperature and vapor pressure. There was no attempt, however, to establish a quantitative relation between the incidence of disease and the climatic variations.

One of the reasons for such a lack of more definite results lies, undoubtedly, in the lack of any adequate theoretical background for planning the necessary observations or experiments. It is the purpose of this note to suggest a working hypothesis which, when developed into a theory, will suggest some quantitatively verifiable relations.

Available qualitative observations indicate that the incidence of some diseases is related to *sudden* changes of climatic variables such as temperature, regardless of the direction of the change. For definiteness we shall discuss here only the temperature as a climatic variable. *Mutatis mutandis,* this reasoning may be applied to other variables.

A rather superficial analogy to the phenomena of nerve excitation under the action of sudden changes in electric currents suggests the possibility of a formal application of a "two-factor theory" to our problem.

Suppose that there are two physiological factors, a and b, which determine the normal functioning of some parts of our organism. Let the organism function normally when the two factors are in a given constant ratio, which, without loss of generality, may be assumed to be unity. Hence, for normal functioning, we require

$$a = b . \tag{1}$$

Whenever $a \neq b$, the organism is not functioning properly, its resistance to disease is lowered, and the incidence of disease increases with increasing absolute value $|a - b|$. At a first approximation we may consider the incidence Idt of a given disease during the interval dt of time to be proportional to $|a - b|dt$, so that, with α as a coefficient,

$$Idt = \alpha|a - b|dt . \tag{2}$$

Denoting by T the temperature and by K, M, k, and m four constants, let the variations of a and b with time be given by the following differential equations:

$$\frac{da}{dt} = KT - ka, \quad \frac{db}{dt} = MT - mb \tag{3}$$

with

$$\frac{K}{k} = \frac{M}{m} = \kappa. \tag{4}$$

If the temperature is kept at a constant value T for a sufficiently long time, a and b will reach their asymptotic values:

$$a = b = \frac{K}{k} T = \frac{M}{m} T = \kappa T. \tag{5}$$

If, at the moment $t = 0$, the temperature is suddenly changed by an amount $T_1 \gtrless 0$, now becoming equal to $T + T_1$, then, from that moment on, a and b will vary according to the equations

$$a = \kappa T + \kappa T_1 (1 - e^{-kt}) \tag{6}$$

and

$$b = \kappa T + \kappa T_1 (1 - e^{-mt}). \tag{7}$$

Hence

$$|a - b| = \kappa |T_1 (e^{-mt} - e^{-kt})|. \tag{8}$$

As t tends to infinity $|a - b|$ tends to zero. As is readily seen from (8) the quantity $|a - b|$ has a maximum for

$$t = \frac{1}{m - k} \log \frac{m}{k} > 0. \tag{9}$$

Now let a continuous change in temperature be represented by

$$T_1(t) = T_1^* (1 - e^{-\lambda t}), \tag{10}$$

so that the total temperature now is $T + T^*(t)$ where T_1^* and λ are constants and $T_1^* \gtrless 0$. Introducing (10) into (3) and integrating with the initial condition

$$a = b = \kappa T \quad \text{for } t = 0, \tag{11}$$

we find

$$a = \kappa T + \kappa T_1^* (1 - e^{-kt}) - \frac{K T_1^*}{k - \lambda} (e^{-\lambda t} - e^{-kt}) \tag{12}$$

and

$$b = \kappa T + \kappa T_1^* (1 - e^{-mt}) - \frac{M T_1^*}{m - \lambda} (e^{-\lambda t} - e^{-mt}). \tag{13}$$

If

$$\lambda >> k, \tag{14}$$

then

$$\left| \frac{KT_1^*}{k-\lambda} \right| << \kappa T_1^*. \tag{15}$$

Hence in this case the last term in equation (11) is small compared to the preceding one. As λ increases that term decreases. The same holds true of the last term of (12). For sufficiently large values of λ, equations (12) and (13) reduce correspondingly to (6) and (7), as should be the case physically. For sufficiently slow variations of T, when λ is not too large, equations (12) and (13) may be conveniently used.

If, on the other hand, λ is very small, then (12) and (13) reduce correspondingly to:

$$a = \kappa T + \kappa T_1^*(1 - e^{-\lambda t}); \tag{16}$$

$$b = \kappa T + \kappa T_1^*(1 - e^{-\lambda t}); \tag{17}$$

so that $a = b$ all the time. A sufficiently slow variation of T does not result in a physiological disturbance nor in an increased susceptibility to disease.

From equation (2) it follows that total incidence of disease during the time following a sudden change in temperature will be proportional to

$$\int_0^\infty |a - b| \, dt. \tag{18}$$

It follows from (8) that the integral (18) in its turn is proportional to κT_1 or to $\kappa \Delta$, if we now denote the sudden change in temperature by Δ. For practical purposes the upper limit of integration may be taken as $1/nl$, where l is the smaller of the two quantities, k and m, and n is of the order of 3 or 4.

Absolutely sudden changes do not actually occur. But, if we make a plausible guess that $a \sim b \sim \text{day}^{-1}$, then we may consider a strong hourly variation as sufficiently sudden. Let $N(\Delta)d\Delta$ be the distribution function of the absolute values of hourly Δ's which have been observed over a sufficiently long period, so that $N(\Delta)d\Delta$ denotes the number of variations whose value is between Δ and $\Delta + d\Delta$, regardless of the sign of Δ. We may now write the following for the total incidence I of disease during the period:

$$I = \alpha \int_0^\infty \Delta N(\Delta) d\Delta = \alpha \bar{\Delta}, \tag{19}$$

where $\bar{\Delta}$ denotes the average hourly variation during the period.

Hence, under the above assumption, as expressed by equations (2), (3), and (4), we find a direct proportionality between the incidence of disease and the average hourly variation $\bar{\Delta}$. Both can be measured directly.

The procedure thus indicated by the theory is to look not for individual temperature variations and correlate them with individual cases of incidence of disease, but to determine the incidence of disease for various periods of the year, for which periods the average hourly variations of temperature are sufficiently different, and to see whether the predicted linear relation holds.

If we assume that the incidence Idt is not proportional to $|a - b|\, dt$ but is some more general function

$$Idt = F(a - b)\, dt \tag{20}$$

then, by introducing (6) and (7) into (18) and integrating with respect to t from 0 to ∞, we find the incidence per sudden change as a function $U(\Delta)$. Then, instead of (19), we find

$$I = \alpha\, \overline{U(\Delta)}. \tag{21}$$

The function $\overline{U(\Delta)}$ can be determined from the empirically observed $N(\Delta)$.

We may make a more general assumption, namely,

$$Idt = \alpha[|a - b| - h]\, dt, \tag{22}$$

where h is a threshold, so that $Idt = 0$ for $|a - b| \leqslant h$. Such a relation is particularly likely to hold for the incidence of death, though it may hold also for the incidence of disease. The total incidence $I(\Delta)$ which results from a sudden change Δ is now given by

$$I(\Delta) = \int_{t_1}^{t_2} [|a - b| - h]\, dt, \tag{23}$$

where t_1 and t_2 are the roots of the equation

$$|a(t) - b(t)| = h. \tag{24}$$

From (6) and (7) it follows that equation (24) has roots only when $\Delta > h/\eta$, where η is the maximum value of $\kappa|e^{-mt} - e^{-kt}|$, obtained by introducing (9) into it. Hence $I(\Delta)$ is also a function of h, so that

$$I = V(\Delta, h). \tag{25}$$

Consequently, we have for a long period

$$I = \overline{V(\Delta, h)}. \tag{26}$$

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NETS WITH DISTANCE BIAS

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A distance bias is imposed on the probability of direct connection between every pair of points in a random net. The probability that there exists a path from a given point in the net to another point is now a function of both the axone density and the distance between the points. A recursion formula is derived in terms of which this probability can be computed.

The rate of spread of an epidemic where probability of contact depends on the distance between the individuals can also be computed from the recursion formula.

Using an approximation method, R. Solomonoff and A. Rapoport (1951, see pp. 107–17) have deduced an equation which implicitly defines γ, the weak connectivity of a random net as a function of its axone density, i.e., the average number of axones issuing from each point. It was shown how the weak connectivity was a measure of the probability that an arbitrary individual in a closed population succumbs to a contagious disease introduced by a single infected individual, where it is assumed that the disease has a finite contagious period, followed by immunity or death, and where contacts between any pair of individuals are assumed equiprobable.

To make the epidemic picture more realistic, it is obviously necessary to introduce some sort of "distance bias," i.e., a distribution governing the probability that a given individual will come in contact with another given individual in the population. Such probability cannot in general be assumed constant, since individuals are more likely to come in contact with some individuals than with others. A constant probability of encounter represents the extreme case of very thorough "mixing."

Assuming the approximation method of Solomonoff and Rapoport valid, we shall derive a procedure for computing $\gamma(r)$, the probability that an individual at a distance r from the original source of infection will eventually contract the disease, if the probability of

contact of two individuals is governed by a function of the distance between them.

In terms of a neural net, $\gamma(r)$, will indicate the probability that there exists a path from a neuron to another neuron at a distance r.

In order to generalize the result of the above-mentioned paper (Solomonoff and Rapoport, 1951), we will give another derivation of equation (20) of that paper, which, incidentally, will enable us to compute the rate of spread of the epidemic (or, in terms of the neural net, the expected number of neurons t axones removed from the given one).

We will again follow the axone-tracing procedure described in the above paper. Let $p(t)$ designate the probability that a given neuron is contacted on the tth tracing (whether or not it had been contacted on previous tracings). Note that in the absence of distance bias, the p's represent independent events, since being contacted on one tracing does not affect the chances of being contacted on another tracing. Likewise if $q(t) = 1 - p(t)$, the q's are independent probabilities.

Then the probability that a neuron is contacted *for the first time* on the tth tracing will be

$$p(t) \prod_{i=0}^{t-1} q(i) = [1 - q(t)] \prod_{i=0}^{t-1} q(i). \tag{1}$$

Since each neuron sends on the average a axones, and there are N neurons in the net, the expected number of axones to be traced on the $(t + 1)$th tracing will be

$$aN[1 - q(t)] \prod_{i=0}^{t-1} q(i). \tag{2}$$

The probability that any neuron in the aggregate is *not* contacted by any of these axones on the $(t + 1)$th tracing will then be

$$q(t+1) = (1 - 1/N)^{aN[1-q(t)] \prod_{i=0}^{t-1} q(i)}, \tag{3}$$

which for large N can be written as

$$q(t+1) = \text{Exp}\left\{ -a\,[1 - q(t) \prod_{i=0}^{t-1} q(i) \right\}$$

$$= \text{Exp}\left\{ -a \left[\prod_{i=0}^{t-1} q(i) - \prod_{i=0}^{t} q(i) \right] \right\}. \tag{4}$$

Taking a product of both sides of (4) with respect to t, we obtain

$$\prod_{j=1}^{t+1} q(j) = \prod_{j=1}^{t} \operatorname{Exp}\left\{ -a \left[\prod_{i=0}^{j-1} q(i) - \prod_{i=0}^{j} q(i) \right] \right\}$$

$$= \operatorname{Exp}\left\{ -a \sum_{j=1}^{t} \left[\prod_{i=0}^{j-1} q(i) - \prod_{i=0}^{j} q(i) \right] \right\} \tag{5}$$

$$= \operatorname{Exp}\left\{ -a \left[q(0) - \prod_{i=0}^{t} q(i) \right] \right\}.$$

But $q(0) = (N-1)/N \sim 1$ for large N. Therefore, since

$$\lim_{t\to\infty} \prod_{j=1}^{t+1} q(j) = \lim_{t\to\infty} \prod_{j=0}^{t} q(j) = 1-\gamma, \tag{6}$$

we have, taking the limit of both sides of (5), as t approaches infinity,

$$1-\gamma = e^{-a\gamma} \quad \text{or} \quad \gamma = 1-e^{-a\gamma}, \tag{7}$$

which is equation (20) of the above-mentioned paper.

Let us now introduce a probability density $f(r)$, such that $f(r)\,dS$ will denote the probability that an axone will contact a neuron *in the vicinity* of a point at a distance r from the neuron which sent out the axone. Here dS is a differential of length, area, or volume, depending on the dimensionality of our net. Evidently we must have

$$\int_S f(r)\,dS \leqq 1, \tag{8}$$

where the integration is taken over the space occupied by the net.

To fix ideas, let our net be one-dimensional and let us choose the origin at the point where the tracing of neurons is to start. Then $f|x - x_0|\Delta x$ will denote the probability that an axone issuing from the neuron at x_0 will synapse on a neuron *in the vicinity* of the point x, or vice versa.

We wish to extend the method which we used to derive $\gamma(a)$ as a function of axone density a, to a derivation of $\gamma(a,x)$, or, since a is fixed, of $\gamma(x)$. That is to say, we seek the probability that there exists a path through any number of internuncials from a neuron taken at the origin to a neuron in the vicinity of x, where distance bias has been imposed by the function $f|x - x_0|$.

However, the method used above is not immediately generalizable to the case with distance bias, because when distance bias is introduced, the p's and hence the q's are no longer independent. To show this, assume there is a bias in favor of the nearer neurons

being contacted on each tracing (i.e., bias in favor of shorter axones). Then if the probability of being contacted on a particular tracing is high, this means that many neurons in the immediate vicinity will be contacted, some of them for the first time. And this in turn means that many axones will be traced from the immediate vicinity on the next tracing. Hence being contacted on some tracing enhances the probability of being contacted on subsequent tracings.

To avoid this difficulty, we shall rewrite equation (3) in terms of another probability $P(t)$, which will be defined as the probability of being contacted *for the first time* on the tth tracing. By equation (1) we have

$$P(t) = [1 - q(t)] \prod_{i=0}^{t-1} q(i). \tag{9}$$

It also follows from the definition of $P(t)$ that

$$\left[1 - \sum_{j=0}^{t} P(j) \right] q(t+1) = 1 - \sum_{j=0}^{t+1} P(j), \tag{10}$$

$$q(t+1) = \left[1 - \sum_{j=0}^{t+1} P(j) \right] \left[1 - \sum_{j=0}^{t} P(j) \right]^{-1}, \tag{11}$$

$$1 - q(t+1) = P(t+1) \left[1 - \sum_{j=0}^{t} P(j) \right]^{-1}. \tag{12}$$

Rewriting equation (4) in terms of P's, we then obtain

$$P(t+1) = \left[1 - \sum_{j=0}^{t} P(j) \right] (1 - e^{-aP(t)}). \tag{13}$$

Equation (13) is a recursion formula for the P's which allows the calculation of all successive P's once the first is known. The total number of neurons contacted by the tth tracing is evidently

$$N \sum_{j=0}^{t} P(j).$$

In terms of the epidemic this function measures the spread of the epidemic (total number who have succumbed at time t). Furthermore we have

$$\sum_{j=0}^{\infty} P(j) = \gamma. \tag{14}$$

In contrast to equation (4), equation (13) is generalizable to the case with distance bias. Let ρ be the linear density of neurons

in our net. Subdivide the net into "macroscopically" small regions Δx, analogous to those considered in the kinetic theory of gases. That is, the regions are small compared to the extent of the net but each region contains a great number of neurons. Then the expected number of neurons contacted on the tth tracing for the first time in the region Δx about the point x will be $\rho P(x,t)\,\Delta x$. Consequently the expected number of axones to be traced from that region will be $a\rho P(x,t)\,\Delta x$. The probability that a neuron at x_0 is *not* contacted by any axone issuing from any region on the $(t+1)$th tracing will be

$$\prod_x \left[\, 1 - f|x - x_0|\Delta x \,\right]^{a\rho P(x,t)\Delta x} \tag{15}$$

where the product is taken over all the regions Δx, taking a representative point x from each region. Therefore the probability that a neuron at x_0 will be contacted by at least one axone on the $(t+1)$th tracing will be

$$1 - \prod_x \left[\, 1 - f|x - x_0|\Delta x \,\right]^{a\rho P(x,t)\Delta x}. \tag{16}$$

Now the probability that the neuron at x_0 had not been contacted on a previous tracing is

$$1 - \sum_{j=0}^{t} P(j). \tag{17}$$

Furthermore the events represented by the probabilities (16) and (17) are now independent, since the distribution of axones to be traced is now given in terms of the distance bias. Therefore the product of the probabilities (16) and (17) gives us

$$P(x, t+1) = \left[\, 1 - \sum_{j=0}^{t} P(j) \,\right] \left\{ 1 - \prod_x \left[\, 1 - f|x - x_0|\Delta x \,\right]^{a\rho P(x,t)\Delta x} \right\}, \tag{18}$$

which is the generalization of (13) desired. In the case without distance bias, where $\rho\Delta x = 1$ and $f|x - x_0|\Delta x = 1/N$, equation (18) reduces to (13), as it should.

Equation (18) is a recurrence formula for the $P(x, t)$. Having calculated the successive $P(x, t)$, we obtain $\gamma(x)$ from the relation

$$\gamma(x) = \sum_{t=0}^{\infty} P(x, t). \tag{19}$$

Critique of the Method. The above method fails if the density of neurons is too low, and/or the distance bias is too strong. These two parameters have a definite relation to each other. If, for example, the distance bias is weak, that is the probability of direct connection is fairly constant over considerable intervals, then we may artificially increase the density of the neurons by taking Δx larger. But if both the density is low and the bias strong, we cannot take larger intervals without committing gross error, because in our treatment the probability of direct contact was considered constant throughout an interval.

To illustrate this we shall take an extreme case, namely where direct contact is possible only between two adjacent neurons. Then we are forced to take Δx so that it contains only one neuron. Starting our tracing procedure from the origin, we see that successive neurons to the right of the origin will be contacted on successive tracings only as long as not all axones of a neuron will go to the left. The probability that this event will not occur is evidently $(1 - 2^{-a})$, and the probability that it will not occur t successive times is $(1 - 2^{-a})^t$. Hence $(1 - 2^{-a})^{t_2 - a}$ is the probability that a path exists to exactly t neurons to the right of the origin. The expected number of neurons to which a path exists will then be given by

$$N\gamma = \frac{2}{2^a} \sum_{t=0}^{N} t(1-2^{-a})^t, \tag{20}$$

counting both the neurons to the right and to the left of the origin. For N very large, the expected number of neurons to which a path exists remains finite, namely,

$$\frac{2}{2^a} \sum_{t=0}^{\infty} tA^t = \frac{2}{2^a}\left[\, 1 + \frac{A}{(1-A)^2} \,\right], \tag{21}$$

where $A \equiv (1 - 2^{-a})$. This gives for the expected number of neurons

$$\frac{2}{2^a}\left(1 + \frac{1-2^{-a}}{2^{-2a}}\right) = 2(2^a + 2^{-a} - 1)\,.*$$

It can be shown that this result cannot be obtained from equation (18) by setting $\rho = \Delta x = 1$ and putting for $f|x - x_0|$ the value $1-2^{-a}$ for $x - x_0 = 1$ and zero otherwise. The reason for this lies

*For small values of a it is important to correct the quantity on the right side of (22) by subtracting unity, since the neuron at the origin was counted twice.

in the fact that in our treatment it was supposed that at each tracing a number of neurons were contacted in each region and that probability of contact was constant throughout a small region. In the extreme case just treated, however, a neuron was either contacted or not, and the neuron was coextensive with the region. If a neuron was contacted, the same number of axones were traced on the next step; if it was not contacted, the tracing stopped altogether. The discrepancy is analogous to the one observed in the theory of radiation of a black body, which made necessary the postulate of discontinuous radiation. So long as the density of the neurons is sufficiently great and/or the distance bias sufficiently weak, the connectivity problem can be treated as a continuous case.

Our model of the net with distance bias actually assumes a subdivision of the net (or the community in the contagion model) into a number of subnets (or subcommunities) such that within each subcommunity contacts are equiprobable, but *inter*community contact is governed by a distance bias. The picture is not too far-fetched if the subcommunities are regarded as "households" where thorough mixing of contact occurs.

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RESONANCES OF BIOLOGICAL CELLS AT AUDIBLE FREQUENCIES*

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Two theories are discussed to account for the observed resonances of biological cells at sonic frequencies. One theory assumes the cell wall to be a stretched balloon surrounded by, and filled with, an incompressible fluid. The other treats the cell wall as a rigid shell. Both lead to reasonable physical constants for the cell wall.

Introduction. The biological effects of intense sound waves in liquids have been a subject of interest for many years. Aqueous suspensions are dramatically altered by brief exposures to intense sonic fields; protozoans, algae, and bacteria are destroyed; red blood corpuscles are torn into fragments; and small animals are killed (Chambers and Harvey, 1931). In almost all experiments the occurrence of cavities in the liquid has accompanied the destructive effects. There seems little doubt that the destructive results of intense acoustic fields in liquids are produced by the shearing forces in the immediate neighborhood of these cavities.

Qualitatively, the same results are obtained at 1 kc./sec. and at 1 mc./sec. (Chambers and Gaines, 1932). Most studies have been carried out at an isolated set of frequencies, and little attempt has been made to measure the intensities of the acoustic field. A study, reported in another journal, shows that there are optimum frequencies at which the breakdown occurs much more rapidly for a fixed intensity. These frequencies depend on the type and size of the or-

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ganism treated. Table I shows the physical sizes and the optimum breakdown frequencies for several strains of paramecium.

TABLE I

SPECIES	$2\bar{a}$	$2\bar{b}$	$\bar{a}$ eff.	$\bar{a}/h$	ν obs.
P. caudatum	222.6μ	63.0μ	71.4μ	8.3	1.2 kc./sec.
P. busaria	117.2	51.4	41.6	9.8	1.7
P. calkensi	125.6	56.2	45.4	6.2	1.9
P. aurelia G's	123.8	29.2	39.8	6.9	3.3
P. aurelia 51	127.8	30.2	38.2	6.8	3.5
P. aurelia 81a	98	38	34.0	5.0	4.1
P. trichium	79.6	37.5	29.2	—	7.2

Physical sizes and resonant frequencies of seven strains of Paramecium species. $2a$ is the longest diameter; $2b$ is the longest diameter at right angles to $2a$. The effective radius a equals $a+b/2$; h is the thickness of the cell cortex. All figures are the average sizes of at least twenty individuals.

The wave length of sound in water at 1 kc./sec. is 1.5 meters, i.e., about 10^4 times larger than the average P. caudatum cell. Thus the resonances producing increased breakdown must be due to properties of the cell itself. As the breakdown does not occur in the absence of cavitation, and as the cavities occur most readily outside the cell (Harvey, 1947), it seems reasonable to assign these resonances to the properties of the cell membrane. Hence these resonances offer a method of investigating the elastic properties of the cell membrane (or possibly the cell cortex).

To actually assign any significance to these optimum breakdown frequencies, the cell must be interpreted in terms of a simpler physical model. The present paper deals with the mathematical development of two such models, both of which make resonances reasonable in the observed frequency range. The first model treats the cell membrane as one possessing an interfacial tension, but no rigidity. This model has been used in many previous studies (Harvey, 1938), although the methods used could not be applied to the cells considered here. The second cell model to be considered assigns a rigidity to the cell cortex. In both models the cells are considered to be spherically symmetric, to be filled with an ideal, incompressible liquid, and to be surrounded by another similar liquid. Clearly the paramecia do not have spherical symmetry, and the viscosity of the cell contents is certainly important. Thus the present development is only a first approximation.

Interfacial Tension Waves. As noted above, this first model replaces the cell by a spherical shell, lacking any rigidity, but possessing an interfacial tension. It makes no difference if this tension is a true liquid-liquid interfacial tension (as that between water and oil), or a liquid–membrane tension, or a tension residual in a stretched membrane (such as a rubber balloon). Physically all of these may exist at the cell boundary. Values of this interfacial tension, T,* measured on large non-mobile cells, range from 0.01 to 3.0 dynes/cm. The theory discussed here gives values of T from 3 to 10 dynes/cm. for paramecia.

The shapes of the paramecia are far too complex to handle mathematically. Even the simpler model of a prolate spheroid presents real difficulties. Rather than become lost in the details of a closer approximation, it seems wise to consider the simple case of a spherical cell. In the case of the electromagnetic wave equations, this symmetry approximation does not alter the order of magnitude of the sizes of resonant conductors. It appears reasonable to assume that the same thing would be true here.

As the compressibility of the liquids is ignored in this treatment, the starting point is not the acoustic wave equations which depend on the compressibility of the liquids for their existence. In any event these acoustic waves are many orders of magnitude too large. Surface tension waves of a liquid have a much shorter wave length than acoustic waves. The discussion of interfacial tension waves is similar to that of surface tension waves. The appropriate equations of motion for an ideal incompressible liquid can be found in many texts. The notation used here is similar to L. Page's (1935).

The liquid motions are assumed to be irrational and only relatively small velocities are permitted. Page shows that these motions can be described by the following equations:

$$\boldsymbol{v} = -\nabla\Phi; \tag{1}$$

$$\nabla^2\Phi = 0; \tag{2}$$

$$\dot{\Phi} = p/\rho + \Omega + f(t). \tag{3}$$

In these $\boldsymbol{v}$ is the vector velocity, Φ the velocity potential, p the pressure, ρ the density, Ω the potential energy per unit mass, and $f(t)$ is an arbitrary function of t, the time. Since only the spatial derivatives of Φ have any physical significance, we choose

*For a complete list of symbols, see pages 104–05.

$$f(t) = 0 .$$

The only potential energy in this problem is that due to gravity, i.e.,

$$\Omega = g\, h .$$

Since this is approximately constant over a small cell, it may be ignored in a problem involving alternating pressures and velocities.

Quantities inside the cell will be designated by the subscript i, those outside by the subscript 0. Standard spherical coordinates r, θ, and ψ will be used. All equations, from this point on, will refer to the time dependent portions of v, Φ, and p. In particular, equation (3), the equation of motion, can be rewritten as

$$\left.\begin{aligned} \dot{\Phi}_i &= p_i/\rho_i \\ \dot{\Phi}_0 &= p_0/\rho_0 \end{aligned}\right\} . \tag{4}$$

The above are general hydrodynamic relationships. Now consider the specific cell model. The liquids, being ideal, may slip freely over the membrane but not lose contact with it. Let a be the radius of the equilibrium position of the spherical membrane, possessing the interfacial tension T. Assume a small deformation which carries the point (a, θ, ψ) to $(a + R, \theta, \psi)$, where R, the radial extension, depends on θ and ψ. The excess force per unit area on the membrane in the $+r$ direction is

$$\left.\begin{aligned} F &= \frac{T}{a^2 \sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta\frac{\partial R}{\partial\theta}\right) + \frac{T}{a^2\sin^2\theta}\frac{\partial^2 R}{\partial\psi^2} . \\ &\text{Hence we find} \\ p_i &= \rho_0 - F . \end{aligned}\right\} \tag{5}$$

Other boundary conditions are: a) the center of the cell stands still; b) no effects of the motion are observed as $r \to \infty$; c) the liquid adheres to the membrane at all points and at all times. This last condition will be satisfied if the liquid radial velocity is continuous across the membrane. Expressed analytically these conditions are:

a) $$\frac{\partial \Phi_i}{\partial r} = 0 \qquad \text{at} \qquad r = 0; \tag{6}$$

b) $$\Phi_0 \to 0 \qquad \text{as} \qquad r \to \infty; \tag{7}$$

c) $$\frac{\partial \Phi_i}{\partial r} = \frac{\partial \Phi_0}{\partial r} \qquad \text{at} \qquad r = a. \tag{8}$$

A displacement of the membrane in the θ or ψ direction would contribute nothing since the membrane lacks rigidity. As an added simplification for this model assume that Φ_i, Φ_0, and R are independent of ψ.

An appropriate solution for equations (2), (6), and (7) is:

$$\left.\begin{aligned} \Phi_i &= \sum_{n=0}^{\infty} A_n r^n e^{j\omega_n t} P_n(\cos\theta), \\ \Phi_0 &= \sum_{n=0}^{\infty} B_n r^{-(n+1)} e^{j\omega_n t} P_n(\cos\theta), \end{aligned}\right\} \tag{9}$$

where A_n, B_n, and ω_n are constants and $P_n(\cos\theta)$ is the nth Legendre polynomial of argument $\cos\theta$. The constant ω_n is 2π times the characteristic frequency of the nth mode.

Substituting equation (9) into (8) gives us

$$B_n = -\frac{n}{n+1} a^{2n+1} A_n. \tag{10}$$

We now combine (4) and (5) to eliminate the pressures and get

$$\begin{aligned} \dot{\Phi}_i = p_i/\rho_i &= \frac{p_0}{\rho_i} - \frac{T}{a^2 \rho_i \sin\theta} \frac{\partial}{\partial\theta}\left(\sin\theta \frac{\partial R}{\partial\theta}\right) \\ &= \frac{\rho_0}{\rho_i}\dot{\Phi}_0 - \frac{T}{a^2 \rho_i \sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta \frac{\partial R}{\partial\theta}\right). \end{aligned}$$

Differentiating this with respect to time, and using (1) to eliminate R, we get

$$\ddot{\Phi}_i = \frac{\rho_0}{\rho_i}\ddot{\Phi}_0 - \frac{T}{a^2 \rho_i \sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta \frac{\partial^2 \Phi_i}{\partial r\,\partial\theta}\right).$$

To eliminate the velocity potentials, we substitute (9) and then (10) into the last equation as follows:

$$-\omega_n^2 A_n a^n = -\omega_n^2 B_n a^{-(n+1)} - n^2(n+1)\frac{T}{\rho_i A^3} a^n A_n,$$

$$-\omega_n^2\left(1+\frac{n}{n+1}\frac{\rho_0}{\rho_i}\right)=\frac{T}{\rho_i}\left(\frac{n}{a}\right)^3\left(1+\frac{1}{n}\right).$$

In a resonant vibration, one frequency, ω_n, will dominate the motion; only one value of n will be important. The values 0 and 1 for n are prohibited by equation (6). The lowest resonant frequency corresponds to $n = 2$; it is the solution of:

$$\omega_2^2=\frac{T}{\rho_i}\left(\frac{2}{a}\right)^3\left(3/2\right)\left(1+\frac{2}{3}\frac{\rho_0}{\rho_i}\right)^{-1}. \qquad (11)$$

To apply this to paramecia, we choose $\rho_i = \rho_0 = 1$ gm./cc. and find

$$\omega_2^2 = 7.2\, T\, a^{-3}.$$

The —3/2 power relationship seems unusual, but for surface tension waves on water of frequencies near 1 kc./sec. we have

$$\omega^2=\frac{T_s}{\rho}\left(\frac{2\pi}{\lambda}\right)^3,$$

where λ is the wave length and T_s is the surface tension. (For any given wave velocity, there are two wave lengths possible. Only the shorter one corresponds to real waves at frequencies of the order of magnitude considered here.)

The above formula for ω_2 may be used to calculate the values of T for the various paramecium strains. The results assign a value of $T = 3$ dynes/cm. to P. caudatum, and $T = 10$ dynes/cm. to P. trichium. It was originally hoped that these would be closer to one another, but there is no a priori reason to assume that all species, or even all strains of the same species, should have the same interfacial tension, T.

Rigid Shell Shear Waves. The experiments measuring interfacial tensions on non-mobile, or slowly moving, cells can be interpreted in ways other than the usual one; some as measuring the tensile strength of the membrane and others as measuring the rigidity of the cell cortex. The optimum breakdown frequencies of paramecia can also be interpreted as resonant vibrations of a rigid spherical shell, emersed in, and filled with, incompressible liquids. Several modes of vibration will be considered for this model.

Lord Rayleigh (1890), points out in his chapter on rigid shells, that there are, in general, two types of vibrations possible. The more common type involves no extension of the mid-surface; it is the mode usually discussed for flat plates and bells. However, according to a theorem due to Jellet, no closed convex surface can be deformed in any way without extension (or compression) of the mid-surface. Therefore, the usual methods of treating shells are valueless here.

For vibrations with extension of the mid-surface, both the kinetic and the potential energies are proportional to the shell thickness, h. Closed (and almost closed) shells vibrating in air will, therefore, have resonant frequencies which are independent of h. In a cell such as a paramecium it is natural to interpret h as the thickness of the cortical layer.

The rigidity of the cell cortex is negligible compared to steel, glass, or even wood. However, protein gels do have a finite rigidity. Values of the coefficient of rigidity, μ, have been measured for fibrin gels (Ferry and Morrison, 1947). The modes to be discussed here lead to values of μ in the same range as that for fibrin gels, i.e., 10^3 to 10^5 dynes/cm^2.

The analysis follows that of H. Lamb (1882), who fully discussed the vibrations of spherical shells in air. Only modes symmetrical about a diameter will be considered. These fall into two types: 1) those involving tangential motion only; and 2) the modes with both radial and tangential motion.

1) The tangential type of modes will not be affected at all by the intra- and extra-cellular liquids, since these are assumed to be ideal, and hence to slip freely over the cell wall. In this type of motion a point (a, θ, ψ) is carried to $(a, \theta, \psi + \Psi)$. The angular displacement in the ψ direction is Ψ; it is time dependent. Since the liquids play no role, Lamb's analysis for shells in air applies directly to the cell model. He shows that

$$\Psi_n = A_n \frac{d}{d(\cos\theta)} [P_n(\cos\theta)]\, e^{j\omega_n t}$$

and

$$\omega_n^2 = \frac{\mu}{\rho_s a^2} (n-1)(n+2).$$

The subscript s refers to the shell, i.e., ρ_s is the density of the shell. This Ψ mode gives for P. caudatum for $n = 2$, $\mu = 0.8 \times 10^3$ dynes/cm^2. This is in order of magnitude agreement with the fibrin gels; a possible mode.

2) The modes with radial motion as well as tangential involve both the motion of the liquids and that of the shell. A more detailed description of these modes is therefore necessary; it occupies most of the rest of the paper.

Many of the equations from the section on interfacial tension waves may be used without change. The useful ones are (1), (2), (3), (4), (6), (7), and (9). These apply to the liquid motion, and additional equations are necessary to describe the motion of the shell. Changes occur in r and θ; these are denoted by R and Θ. Strains will occur in the r, θ, and ψ directions, and are denoted by e_1, e_2, and e_3 respectively. The average stress on the shell in the $+r$ direction is:

$$-\bar{p}_s = -1/2(p_i + p_0). \tag{12}$$

The accelerating force per unit shell area in the $+r$ direction is:

$$\Delta p_s = p_i - p_0. \tag{13}$$

These last two equations describe analytically the difference between the cell model which is filled with, and surrounded by, incompressible fluids and a shell vibrating in air. In the latter case both $-\bar{p}_s$ and Δp_s must vanish.

The equation used to describe the adherence of the liquids to the membrane in the interfacial tension model, (8), must be modified to:

$$\frac{\partial \Phi_i}{\partial r} = \frac{\partial \Phi_0}{\partial r} + h\dot{e}_1.$$

It will be assumed that $|h\dot{e}_1| << |\dot{R}_s|$; therefore, equations (8) and (10) may be used for this model also. This assumption will be considered at the close of the development; it will rule out one of the solutions as self-inconsistent.

From the geometry of the system (Lamb, 1882), it follows that the strains can be represented by:

$$e_2 = R_s/a + \frac{d\Theta}{d\theta} \tag{14}$$

and

$$e_3 = R_s/a + \Theta \cot\theta. \tag{15}$$

The above equations describe the motion of the liquids, which are similar to those in the interfacial tension model, and also the stresses and strains on the rigid shell. To proceed further the equa-

tions of motion of the shell are needed. These can be derived from Hamilton's principle as follows:

$$\int_{a-h/2}^{a+h/2} h\,\rho_s\,\ddot{R}_s\,\delta\,R_s\,4\,\pi\,r^2\,d\,r = \int_{a-h/2}^{a+h/2}\left[-h\frac{\partial\,\Omega_s}{\partial\,R_s}+\Delta\,p_s\right]\delta\,R_s\,4\,\pi\,r^2\,d\,r,$$

therefore

$$h\,\rho_s\,\ddot{R}_s = -h\frac{\partial\,\Omega_s}{\partial\,R_s}+\Delta\,p_s; \tag{16}$$

and

$$\int_0^{\pi} a^2\,h\,\rho_s\,\ddot{\Theta}_s\,\delta\,\Theta_s\sin\theta\,d\theta = -\int_0^{\pi} a^2\,h\,\delta_{\Theta_s}(\Omega_s)\sin\theta\,d\,\theta; \tag{17}$$

where Ω_s is the elastic potential energy per unit shell volume. Since motion occurs in two directions, there are two equations of motion. It is necessary to find expressions for R_s and Θ so that both equations of motion are simultaneously satisfied.

The radial equation, (16), is treated first. A value is specified for R_s by equations (1), (8), (9), and (10). Combining equations (1) and (9), and integrating with respect to time, gives for the P_n term of R_s:

$$R_s = a\left(\frac{j}{n}\frac{A_n}{\omega_n}a^{n-1}\right)P_n(\cos\theta)\,e^{j\omega_n t}. \tag{18}$$

To find Ω_s it is necessary to know $\bar{p}_s$. Using (3), (4) and (12) gives us

$$\bar{p}_s = \frac{j\,\omega_n}{2}\left(A_n\,a^n\,\rho_i + B_n\,a^{-n+1}\,\rho_0\right)P_n(\cos\theta)\,e^{j\omega_n t}.$$

This can be simplified, with the aid of (10) and (18), and we get

$$\bar{p}_s = j\,\rho_s\,\omega_n^2\,a^2\,C\frac{R_s}{a}, \tag{19}$$

where

$$C \equiv \frac{\rho_i - \dfrac{n}{n+1}\rho_0}{2\,n\,\rho_s}. \tag{20}$$

Likewise, replacing (12) by (13), gives us

$$\bar{p}_s = j\,\rho_s\,\omega_n^2\,a^2\,D\,\frac{R_s}{a}, \tag{21}$$

where

$$D \equiv \frac{\rho_i + \dfrac{n}{n+1}\,\rho_0}{n\,\rho_s}. \tag{22}$$

Hooke's law, applied in the radial direction, is used to eliminate e_1 from Ω_s. The generalized form of Hooke's law applied to this problem gives us the following

$$-p_s = \lambda(e_1 + e_2 + e_3) + 2\,\mu\,e_1,$$

where λ is Lamé's constant. For a shell we find

$$\begin{aligned}\Omega_s &= \frac{\lambda + 2\,\mu}{2}\,(e_1^2 + e_2^2 + e_3^2) + \lambda(e_1e_2 + e_2e_3 + e_3e_1)\\ &= \frac{\bar{p}_s^{\,2}}{2(\lambda + 2\,\mu)} + \mu\left(\frac{\gamma+1}{2}\right)(e_2^2 + e_3^2) + \mu(\gamma - 1)e_2e_3,\end{aligned}$$

where $\gamma = (1+\sigma)/(1-\sigma)$ and $\sigma = \lambda/2(\lambda+\mu)$. Therefore

$$\begin{aligned}\delta\,\Omega_s = \frac{\bar{p}_s}{\lambda + 2\,\mu}\,\delta\,\bar{p}_s &+ \mu[(\gamma-1)e_2 + (\gamma+1)\rho_3]\,\delta\,e_2\\ &+ \mu[(\gamma-1)e_3 + (\gamma+1)e_2]\,\delta\,e_3.\end{aligned} \tag{23}$$

Equations (14), (15), and (23) are used to eliminate e_2, e_3, and Ω_s from (16). This gives us the radial equation of motion:

$$\alpha = \frac{R_s}{a} = 2\,\gamma\left[\frac{d\,\Theta_s}{d\,\theta} + \Theta_s\cot\theta\right], \tag{24}$$

where

$$\alpha \equiv x\left(1 + D\,\frac{a}{h}\right) - 4\,\gamma - x^2\,\frac{\mu}{\lambda + 2\,\mu}\,C^2 \tag{25}$$

and

$$x \equiv \frac{\omega_n^2\,a^2\,\rho_s}{\mu}. \tag{26}$$

Equation (23) can also be used to expand the tangential equation of motion, (17), in terms of e_2 and e_3. After a partial integration with respect to θ of the term involving $\partial e_2/\partial\theta$, and after elimi-

nating e_2 and e_3 by means of (14) and (15), the tangential equation of motion becomes:

$$2\gamma \frac{d}{d\theta}\left(\frac{R_s}{a}\right) = -(x+2)\Theta_s - (\gamma+1)\frac{d}{d\theta}\left[\frac{1}{\sin\theta}\frac{d}{d\theta}(\Theta_s \sin\theta)\right]. \tag{27}$$

The two equations of motion of the shell, (24) and (27), and the expression for R_s, (18), derived from the liquid motion, can all be satisfied simultaneously if, and only if,

$$\Theta_s = \Lambda \frac{dR_s}{d\theta}; \tag{28}$$

and

$$\begin{aligned} \alpha &= -2\gamma n(n+1)\Lambda; \\ 2\gamma &= [-(x+2) + n(n+1)(\gamma+1)]\Lambda; \end{aligned} \tag{29}$$

where Λ is a constant. Eliminating Λ from the last two equations gives us the relationship which specifies the characteristic frequencies:

$$\alpha[-(x+2) + n(n+1)(\gamma+1)] = -4\gamma^2 n(n+1). \tag{30}$$

Finally, substituting the value of α from equation (25) gives us the equations for these characteristic frequencies in terms of x:

$$\begin{aligned} \frac{\mu}{\lambda+2\mu}C^2 x^3 - \left[\left\{n(n+1)(\gamma+1) - 2\right\}\frac{\mu}{\lambda+2\mu}C^2 + 1 + D\frac{a}{h}\right]x^2 \\ + \left[\left(1 + D\frac{a}{h}\right)\left\{n(n+1)(\gamma+1) - 2\right\} \right. \\ \left. + 4\gamma\right]x = 4\gamma[n(n+1) - 2]. \end{aligned} \tag{31}$$

The limiting case $C = D = 0$, reduces this last equation to the equation for the resonant frequencies in air. As a/h is large, the entire character of the roots has been changed. The cube term introduces an extra root. To arrive at numerical results it is assumed that $\sigma = 0.25$ and therefore $\lambda = \mu$. For simplicity, the choice $\rho_0 = \rho_i = \rho_s = 1$ gm./cm.^{3} is also made. The roots of equation (31), for $n = 2$, then are:

$a/h = 10$	$a/h = 5$
${}_a x_2 = 0.22$	${}_a x_2 = 0.35$
${}_b x_2 = 14.5$	${}_b x_2 = 14.9$
${}_c x_2 = 4.6 \times 10^3$	${}_c x_2 = 2.5 \times 10^3$
${}_a \Lambda_2 = 0.24$	${}_a \Lambda_2 = 0.24$
${}_b \Lambda_2 = -6.3$	${}_b \Lambda_2 = -3.6$
${}_c \Lambda_2 = -7 \times 10^{-4}$	${}_c \Lambda_2 = -1.3 \times 10^{-3}$.

The large value of ${}_b\Lambda_2$ for ${}_b x_2$ makes $|h\dot{e}_1| \sim |\dot{R}|$, and in phase with R_s. [This situation might be improved by altering equation (8)]. For the other two roots the assumption that $|h\dot{e}_1| << |\dot{R}|$ is valid.

For both of the self-consistent roots of equation (31) the polar diameter expands as the equator contracts and vice versa. The tangential motion is at right angles to the equator. As the polar diameter contracts, the shell moves away from the pole in the solution represented by the first root, and toward the pole in the other one.

Equation (26) is used to compute values of μ from the characteristic values of x plus the data found in the table. For P. caudatum we find

$${}_a\mu_2 = 1.2 \times 10^3 \text{ dynes/cm.}^2 \quad \text{for } {}_a x_2;$$
$${}_c\mu_2 = 0.8 \quad \text{dynes/cm.}^2 \quad \text{for } {}_c x_2.$$

Thus only the first root gives a reasonable value of μ.

Conclusions. Two different cell models both lead to resonant frequencies for cells the size of paramecium within the observed frequency range. These different modes are illustrated in the figure. The different models and modes could be distinguished, in theory, by their harmonics. The experimental data are not at present sufficiently precise to locate these harmonics.

No mention has been made of the actual cause of cell destruction. It might be due to simple physical rupture, or to heat generated at the antinodes.

SYMBOLS USED

r, θ, ψ = spherical polar coordinates (radius, colatitude and longitude respectively)
R, Θ, Ψ = displacements from equilibrium position
v = vector velocity of the liquid
t = time
$f(t)$ = an arbitrary function of time
$\dot{}$ = A dot over a symbol indicates partial derivative with respect to time
Ω = potential energy per unit mass
Φ = velocity potential
T = surface, or interfacial, tension

p = pressure
ρ = density
$P_n(\cos\theta)$ = the nth Legendre's polynomial of variable $\cos\theta$
ω = 2π times the frequency
a = radius of the sphere
subscript i = inside of sphere
subscript 0 = outside of sphere
subscript s = spherical shell
e_1 = dilitational strain in r direction
e_2 = dilitational strain in θ direction
e_3 = dilitational strain in Ψ direction
λ = Lamé's constant (λ = wave length in equation on surface tension waves from Page)
μ = coefficient of rigidity
σ = Poisson's ratio
$\gamma = (1 + \sigma)/(1 - \sigma)$
$\varkappa = \omega^2 a^2 \rho_s/\mu$
$j = (-1)^{1/2}$

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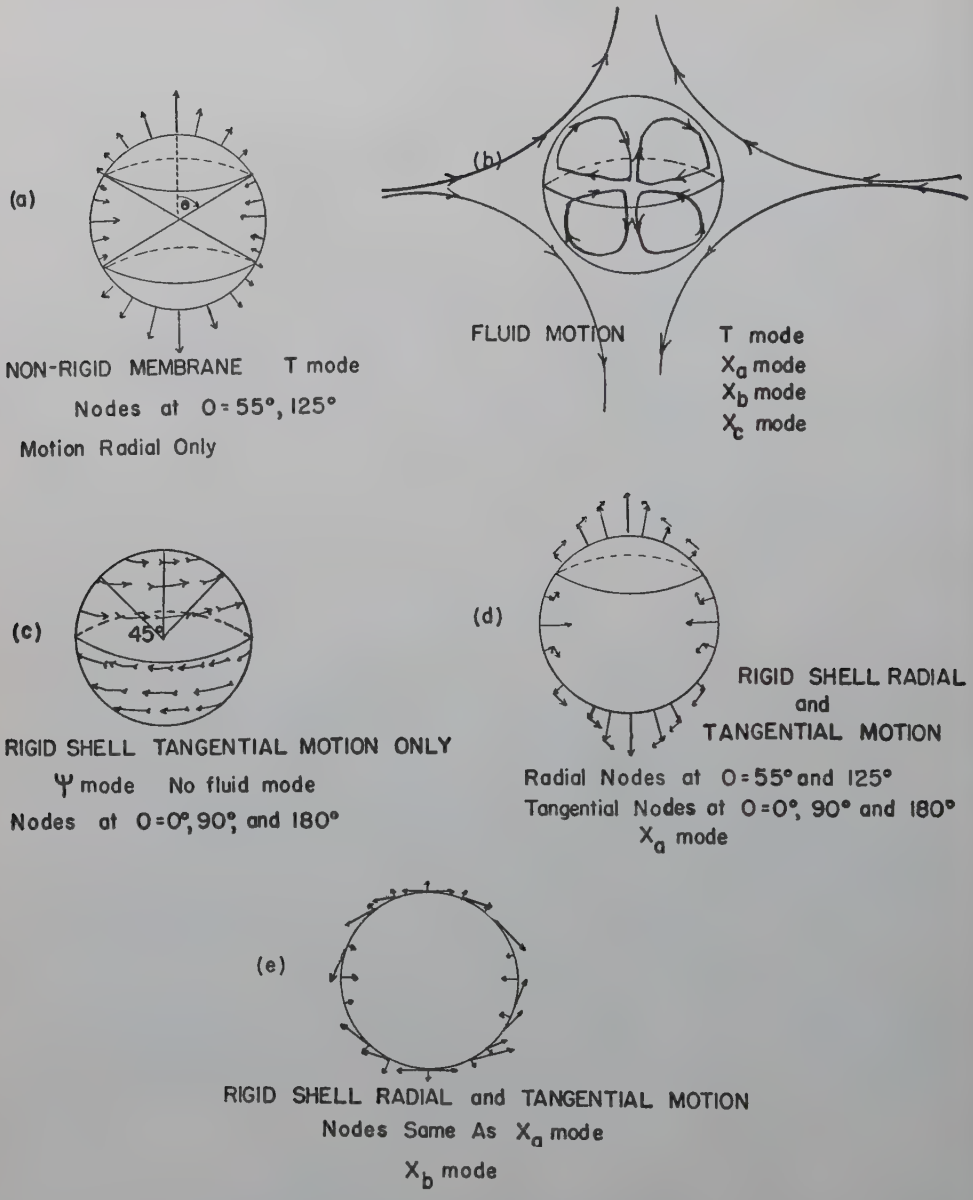

FIGURE 1. The motion of the liquids and cell membrane or cell cortex. These motions are described in detail in the text.

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CONNECTIVITY OF RANDOM NETS

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The weak connectivity γ of a random net is defined and computed by an approximation method as a function of a, the axone density. It is shown that γ rises rapidly with a, attaining 0.8 of its asymptotic value (unity) for $a = 2$, where the number of neurons in the net is arbitrarily large. The significance of this parameter is interpreted also in terms of the maximum expected spread of an epidemic under certain conditions.

Numerous problems in various branches of mathematical biology lead to the consideration of certain structures which we shall call "random nets." Consider an aggregate of points, from each of which issues some number of outwardly directed lines (axones). Each axone terminates upon some point of the aggregate, and the probability that an axone from one point terminates on another point is the same for every pair of points in the aggregate. The resulting configuration constitutes a *random net.*

The existence of a *path* in a random net from a point A to a point B implies the possibility of tracing directed lines from A through any number of intermediate points, on which these lines terminate, to B.

We shall say that B is t axones removed from A, if t is the smallest number of axones contained in any of the paths from A to B. Point A itself is zero axones removed from A. All the other points upon which the axones of A terminate are one axone removed. The points upon which the axones from these latter points terminate, and which are not one or zero axones removed, are two axones removed, etc.

The notion of a random net may be generalized, if it is not assumed that the probability of direct connection between every pair of points in the net is the same. In that case it is necessary to define this probability for every pair of points. This can be done, for example, in terms of the distance between them or in some other way.

If the connections are not equiprobable, we shall speak of a net with a bias.

The following examples illustrate problems in which the concept of a net, defined by the probability of the connections among its points, seems useful.

1. *A problem in the theory of neural nets.* Suppose the points of a net are neurons. What is the probability that there exists a path between an arbitrary pair of neurons in the net? If the net has bias, what is the probability that there exists a path between a specified pair? In particular, what is the probability that a neuron is a member of a cycle (i.e., there exists a path from the neuron to itself through any positive number of internuncials)? Or, one may ask, what is the probability that there exists a path from a given neuron to every other neuron in the net?

2. *A problem in the theory of epidemics.* Suppose a number of individuals in a closed population contract a contagious disease, which lasts a finite time and then either kills them or makes them immune. If the probability of transmission is defined for each pair of individuals, what is the expected number of individuals which will contract the disease at a specified time? In particular, what is the

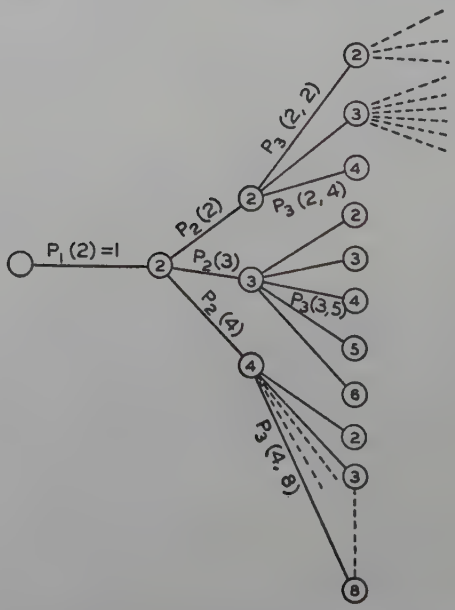

FIGURE 1. The probability tree for the number of ancestors of a single individual.

expected number of individuals which will eventually (after an infinite time) contract the disease? Or else, what is the probability that the entire population will succumb? Note that if the probability of transmission is the same for each pair of individuals, we are dealing with a random net.

3. *A problem in mathematical genetics.* Given the probability of mating between each pair of individuals in a population (as a function of their distance, or kinship, or the like), what is the expected number of ancestors of a given order for each individual? Clearly, the less the expected number of ancestors, the greater the genetic homogeneity of the population.

Each of these problems can be formalized by constructing a "probability tree." As an example, a tree for the genetic problem is illustrated in **Figure 1.**

We note that the tree consists of "nodes" connected by lines. The nodes can be designated by "first order," "second order," etc., depending on their distance from the "root." The number at the node indicates a possible number of ancestors of a given order. The lines connecting the nodes are labeled with the corresponding probabilities. Thus $p_1(2) = 1$, since it is certain that an individual has exactly two ancestors of the first order (parents). However, the parents may have been siblings or half-siblings. Therefore it is possible that the number of grandparents is 2, 3, or 4. The corresponding probabilities are $p_2(2)$, $p_2(3)$, and $p_2(4)$. The probability of having a certain number of great-grandparents depends on how many grandparents one has had. Consequently, those probabilities must be designated by $p_3(i,j)$ where $i = 2, \cdots 4$ and $j = 2, \cdots 8$. In general, the probability of having a certain number of ancestors of order k will depend on how many ancestors of each of the smaller orders one has had. If, however, we simplify the problem by supposing that the probability of having a certain number of ancestors of the kth order depends only on how many ancestors of the $(k-1)$th order one has, then the probability that an individual has exactly n ancestors of the mth order will be given by

$$P_m(n) = \sum_{r=2}^{2^m} \cdots \sum_{j=2}^{8} \sum_{i=2}^{4} p_2(2,i)\, p_3(i,j)\, p_4(j,k) \cdots p_m(r,n). \qquad (1)$$

The expected number of ancestors of the mth order will then be

$$E(m) = \sum_{n=2}^{2^m} nP(n). \qquad (2)$$

Clearly, a similar tree can be constructed for the neural net problem. Here the numbers at the nodes of the kth order would designate the possible number of neurons k axones removed from a given neuron. The p's would designate the corresponding transition probabilities from a certain number of neurons $(k-1)$ axones removed to a certain number k axones removed, etc. If N is the number of neurons in the aggregate, clearly, a neuron B is at most N axones removed from a neuron A, or else there exists no path from A to B. Hence $E(N)$ represents the expected number of neurons in the aggregate to which there exist paths from an arbitrary neuron, if the neurons are not in any way distinguished from each other. This expected number we shall call the *weak connectivity* of a random net and will designate it by γ.

The contagion problem could be formulated in similar terms. Here weak connectivity would represent the expected number of individuals which will contract the disease eventually. If we define Γ, the *strong connectivity* as the probability that from an arbitrary point in a random net there exist paths to every other point, then Γ will represent the probability that the entire population will succumb in the epidemic described above. In this case, the number of "axones" represents the number of individuals infected by a carrier before he recovers or dies.

The weak connectivity of a random net. We shall compute the weak connectivity of a neural net in terms of certain approximations whose justification will be given in subsequent papers. It will be assumed that:

1. The number of axones per neuron a is constant throughout the net. This constant (the axone density) need not be an integer, since it may equally well be taken as the average number of axones per neuron.

2. Connections are equiprobable, i.e., an axone synapses upon one or another neuron in the aggregate with equal probability.

A. Shimbel (1950) has formulated the problem in terms of the following differential-difference equation

$$dx/dt = [N - x(t)][x(t) - x(t-\tau)]. \tag{3}$$

Here $x(t)$ is a function related to the expected number of neurons t axones removed from an arbitrary neuron, and τ is related to the axone density. Then the problem of finding γ is equivalent to the

problem of finding $x(\infty)$. A somewhat generalized form of equation (3) is given also by M. Puma (1939). The solution of the equation is, however, not given.

An approximate expression for γ where N is large was derived by one of the authors (Rapoport, 1948) where the number of axones per neuron is exactly one. This case will be generalized here to a axones per neuron, which are supposed constant through out the aggregate.

The axone-tracing procedure. Let us start with an arbitrarily selected neuron A and consider the set of all neurons removed by not more than t axones from A. Let x be the expected number of these neurons. Then evidently $x = x(N, a, t)$ depends on the total number of neurons in the net, on the axone density, and on t. Moreover, the weak connectivity of the net can be expressed as

$$\gamma(N, a) = x(N, a, N)/N. \tag{4}$$

Since N and a are fixed, we shall refer to the expected number of points removed from A by not more than t axones by $x(t)$. Note that t is a positive integer.

We seek a recursion formula for $x(t)$ which will give us an approximate determination of that function. To give a rigorous treatment of the problem, one would need to deal with distribution functions instead of expected values. For example, $p(i,t)$, denoting the probability that there are *exactly* i neurons not more than t axones removed from A, would determine the distribution for t. Successive distributions (for $t + 1$, etc.) would then depend on previous *distributions,* instead of merely upon the first moments of these distributions (expected values). The "probability tree" method does take these relations into account. An "exact" approach to the problem will be given in a subsequent paper. Meanwhile, however, we shall develop an approximation method in which it will be assumed that the expected value $x(t)$ depends only upon previous expected values, and, of course, upon the parameters of the net.

The recursion formula. We now seek an expression for $x(t + 1) - x(t)$. This is evidently the expected number of neurons *exactly* $(t + 1)$ axones removed from A. We shall make use of the following formula, which may be readily verified. Let s marbles be placed independently and at random into N boxes. Then the expected number of boxes occupied by one or more marbles will be given by

$$N[1 - (1 - 1/N)^s]. \tag{5}$$

In our axone-tracing procedure there are $a[x(t) - x(t-1)]$ axones of the *newly* contacted neurons to be traced on each step. Then the total number of neurons contacted on the $(t+1)$th tracing will be, according to formula (5),

$$N[1-(1-1/N)^{a[x(t)-x(t-1)]}]. \tag{6}$$

But of these neurons the fraction $x(t)/N$ has already been contacted. Hence the expected number of newly contacted neurons will be given by

$$x(t+1)-x(t)=[N-x(t)][1-(1-1/N)^{a[x(t)-x(t-1)]}], \tag{7}$$

which is our desired recursion formula.

Determination of γ. Let us set

$$y(t)=N-x(t). \tag{8}$$

Then equation (7) may be written as

$$y(t+1)=y(t)\,(1-1/N)^{a[y(t-1)-y(t)]}, \tag{9}$$

or

$$y(t+1)\,(1-1/N)^{ay(t)}=y(t)\,(1-1/N)^{ay(t-1)}. \tag{10}$$

Hence

$$y(t+1)\,(1-1/N)^{ay(t)}=\text{constant}=K. \tag{11}$$

We proceed to evaluate K. We have

$$y(t+1)=K(1-1/N)^{-ay(t)}. \tag{12}$$

But $y(t)$ represents the expected number of uncontacted points in the tth step. Since before the tracing began one point constituted the set of contacted points, therefore we have

$$y(0)=N-1, \tag{13}$$

and using formula (5),

$$y(1)=(N-1)^{a+1}N^{-a}. \tag{14}$$

Letting $t=0$ in (12), we obtain

$$K=N^{-aN}(N-1)^{aN+1}. \tag{15}$$

Furthermore, since $y(1) \leqq y(0)$ and $(1-1/N)^{-a} > 1$, we have $y(2) \leqq y(1)$, etc., so that $y(t)$ is a non-increasing function of t (this is also intuitively evident from the definition of y). Since $y \geq 0$ for all t, $y(t)$ must approach a limit as t grows without bound. Hence

$$\lim_{t\to\infty} y(t+1) = \lim_{t\to\infty} y(t) = Y. \tag{16}$$

Note that $\gamma = x(N)$ may also be considered as $\lim_{t\to\infty} x(t)/N$. This is so since contacting no new neurons on any tracing implies that no new neurons will be contacted on any subsequent tracings. If we continue to carry out tracings "symbolically," it is evident that at some tracing not greater than the Nth no new neurons will be contacted, and all subsequent tracings will be "dummy" tracings.

Using equations (12) and (15), we see that Y satisfies the transcendental equation

$$Y = (N-1)(1-1/N)^{a(N-Y)}. \tag{17}$$

For large N, this can be approximated by

$$Y \sim N \operatorname{Exp}\{a(Y/N-1)\}. \tag{18}$$

Hence, for large N,

$$Y/N \sim \operatorname{Exp}\{a(Y/N-1)\}. \tag{19}$$

But $\gamma = x(\infty)/N = 1 - Y/N$. Substituting this value into (19), we obtain the transcendental equation which defines γ implicitly as a function of a, namely,

$$\gamma = 1 - e^{-a\gamma}. \tag{20}$$

We note that for $\gamma = 0$, every a is a solution of (20). If $\gamma \neq 0$, then equation (20) can be solved explicitly for a giving

$$a = \frac{-\log(1-\gamma)}{\gamma}. \tag{21}$$

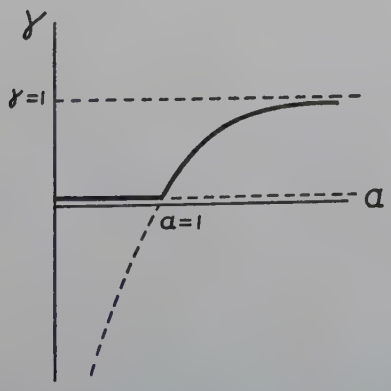

FIGURE 2. Weak connectivity as a function of axone density.

The right side of (21) is analytic in every neighborhood of the origin and tends to unity as γ approaches 0. Expanding that function in powers of γ, we have

$$a = 1 + \gamma/2 + \gamma^2/3 \cdots, \tag{22}$$

which allows us to plot a against γ (cf. Fig. 2). This graph consists of two branches, namely, the entire a-axis and the function (21). Negative values of γ, being physically meaningless, must be discarded. Thus in the region $0 \leqq a \leqq 1$, we have $\gamma \equiv 0$, as is intuitively evident. We must show, however, that for $a > 1$, γ follows the nonzero branch of the graph, otherwise we get the unlikely result that for sufficiently large N the fraction of individuals eventually infected in an epidemic will be negligible, regardless of the number of individuals infected by each carrier of the disease. Actually, the solution $\gamma \equiv 0$ is extraneous for $a > 1$ and appears in our equation because we have let N increase without bound *before* determining the relation between a and γ. In any physical situation N is finite. Hence a physically meaningful procedure is to determine γ as a function of a and N and *then* allow N to increase without bound. Such a function is given by equation (17). Proceeding from that equation we obtain

$$Y/(N-1) = (1-1/N)^{a(N-Y)}, \tag{23}$$

$$\log Y - \log(N-1) = a(N-Y)\log(1-1/N), \tag{24}$$

$$a = \frac{\log Y - \log(N-1)}{(N-Y)[\log(N-1) - \log(N)]}. \tag{25}$$

Let us write $Y = N - \phi(N) = N[1 - \phi(N)/N]$. Then equation (25) may be written as

$$\begin{aligned} &\log N - \log(N-1) + \log[1-\phi(N)/N] \\ &\quad = a\,\phi(N)[\log(N-1) - \log N]. \end{aligned} \tag{26}$$

Since $\phi(N) < N$ for all N, we may expand the last term of the left side of (26) and obtain

$$\begin{aligned} &\log N - \log(N-1) - \phi(N)/N - \tfrac{1}{2}[\phi(N)/N]^2 \\ &\quad - 1/3[\phi(N)/N]^3 \cdots = a\,\phi(N)[\log(N-1) - \log N]. \end{aligned} \tag{27}$$

We now expand $\log(N-1) - \log N$ which appears in the right side of (27) and after rearrangements obtain

$$\log N - \log (N-1)$$
$$= \frac{\phi(N)}{N}\left[1 - a + \frac{\phi(N) - a}{2N} + \frac{[\phi(N)]^2 - a}{3N^2} + \cdots\right] \quad (28)$$
$$< \frac{\phi(N)}{N}\left[1 - a + (1 - \phi(N)/N)^{-1}\right].$$

Now if a is fixed and greater than unity, the limit of $\phi(N)/N$ cannot be zero as N increases without bound, because otherwise for N sufficiently large the right side of (28) becomes negative, while the left side is always positive, a contradiction of inequality (28). Therefore, the limit of Y/N, as N increases without bound, cannot be unity for $a > 1$. But this means that $\gamma \neq 0$ if $a > 1$. Hence, for $a > 1$, the non-zero branch of our curve is the only meaningful one.

An examination of the meaningful part of the graph of equation (20) shows that as long as the axone density does not exceed one axone per neuron, $\gamma = 0$, i.e., for very large N, the number of neurons to which there exist paths from an arbitrary neuron is negligible compared with the total number of neurons in the net. On the other hand, as the axone density increases from unity, γ increases rather rapidly, starting with slope 2. Already for $a = 2$, γ reaches about 0.8 of its asymptotic value (unity) and is within a fraction of one per cent of unity for quite moderate a (say > 6). This means that no matter how large the net is, it is practically certain that there will exist a path between two neurons picked at random, provided only the axone density is a few times greater than unity. The interpretation in terms of an epidemic with equiprobable contacts is entirely analogous.

The case a $= 1$. This case was treated by one of the authors (Rapoport, 1948) by a different method. It was shown that for large N, the probability that a neuron was member of a cycle was given by $\sqrt{\pi/2N}$. This gives the probability of the existence of a path from a neuron over any number of internuncials greater than one to itself. But under the assumption of equiprobable connections, this may well represent the probability of the existence of a path from the given neuron to any *other* neuron in the net. Therefore we should have for large N, in the case $a = 1$,

$$\gamma \sim \sqrt{\pi/2N}. \quad (29)$$

For $N = \infty$, γ reduces to zero, as it should according to equation (20). We shall, however, examine the asymptotic behavior of γ for

large N deduced from our approximate method, in order to compare it with the asymptotic behavior (29) deduced from an exact treatment of the special case. Dividing both sides of (17) by N, we may write for $a = 1$

$$Y/N = [(N-1)/N]^{N-Y+1}, \tag{30}$$

whence, since $Y/N = 1 - \gamma$,

$$\begin{aligned} 1-\gamma &= [(N-1)/N]^{N\gamma+1} \\ &= \mathrm{Exp}\{\ln(1-1/N) + N\gamma\ln(1-1/N)\}. \end{aligned} \tag{31}$$

We let $z = N^{-1}$ and examine the behavior of γ for small values of z. Expanding the right side of (31) by power series and retaining only terms of the second order (note that z and γ vanish together), we obtain

$$\begin{aligned} 1-\gamma = 1 &+ [-z - z^2/2 \cdots] + [-\gamma - \gamma z/2 - \cdots] \\ &+ z^2/2 + \gamma^2/2 + \gamma z + \cdots. \end{aligned} \tag{32}$$

Hence,

$$0 = -z + \gamma^2/2 + \gamma z/2 + \cdots. \tag{33}$$

Differentiating with respect to γ, we get

$$dz/d\gamma = \gamma + \gamma/2 \cdot dz/d\gamma + z/2 + \cdots, \tag{34}$$

$$dz/d\gamma \sim (\gamma + z/2)/(1 - \gamma/2). \tag{35}$$

Therefore $dz/d\gamma$ vanishes at $z = 0$, $\gamma = 0$. Differentiating once again with respect to γ, we obtain

$$\left.\frac{d^2z}{d\gamma^2}\right|_{\substack{z=0\\ \gamma=0}} = 1. \tag{36}$$

Hence the power series representing z as a function of γ begins as follows:

$$z = \gamma^2/2 + \cdots. \tag{37}$$

Thus

$$\gamma^2 \sim 2z = 2/N, \tag{38}$$

$$\gamma \sim \sqrt{2/N} \cong 1.41\sqrt{N}. \tag{39}$$

The "exact" result as expressed by (22) gives

$$\gamma \sim 1.2/\sqrt{N}.$$

Thus the approximate method applied to the case $a = 1$ implies an asymptotic behavior of γ for large N which does not depart too sharply from that deduced by the exact method. The limiting value for γ is zero in both cases. The question of how well the limiting values of γ are approached by the approximate method for $a > 1$ remains open.

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ON SIMULTANEOUS DETERMINATIONS OF THE PERMEABILITY OF A MEMBRANE AND OF THE DIFFUSION COEFFICIENT IN AN ADJACENT MEDIUM

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This paper deals with diffusion into a medium of finite thickness through a flat structure which can be considered either as a slice of tissue or as a membrane. Formulae are given to determine the diffusion coefficients in both the flat structure and the adjacent medium from the knowledge of the amount of substance penetrating the medium. The meaning of the formula: (permeability coefficient) = (diffusion coefficient)/(membrane thickness) and the experimentally observed variability of the permeability coefficient in the non-steady state are interpreted on the basis of the mathematical theory of diffusion.

1. *The background and the objectives of the paper.* There are essentially two methods for the determination of the permeability coefficient. One whose theory was given by D. H. Andrews and J. Johnston (1924) consists of immersing the membrane or the tissue slice in the substance for which the permeability of the tissue is being studied and of measuring the gain in weight of the slice in relation to the duration of the immersion. This method has been used both by chemists and physiologists, particularly in the case of liquids where the gain in weight is more easily determinable than in the case of gases. For the latter the method developed by H. A. Daynes (1920) has been preferred. It consists of letting the gas diffuse *through* the membrane rather than *into* it as in the previously mentioned method. It can be diagrammatically represented as shown in Figure 1. The tissue slice or membrane is bounded by the planes $x = -a$ and $x = 0$. The gas is kept at a constant concentration C in the region $x \leq -a$ and diffuses through the membrane into a container bounded by the planes $x = 0$, $x = b$. The initial concentration of the gas in the slice and in the container is assumed to be zero and the permeability coefficient of the slice is determined from the relationship between the amount of substance accumulating in the container and the duration of the diffusion. The theories of both methods consider the diffusion to be a one-dimensional process. An-

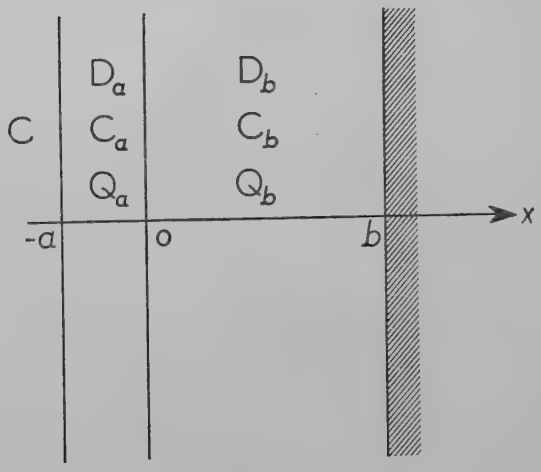

FIGURE 1

drews and Johnston assume the concentrations to be equal on both faces of the slice and constant throughout the experiment, an assumption which is well satisfied if the thickness of the slice is small with respect to the mass of the surrounding liquid. Daynes assumes different concentrations on the two faces of the slice but constant in time, that is, unchanged by the amount of substance diffusing into the container. This latter condition requires either a limitation of the experiment to negligible changes of concentration in the container or the provision of a special arrangement which maintains constant the concentration in it. For instance, the gas diffusing into the container may be removed or its partial pressure may be kept constant in any other manner. In the usual applications of this method the choice is made to fulfill the assumptions of the theory by limiting the measurements to small changes of concentration in the container.

It is the objective of the present paper to show how this limitation can be avoided, so that measurements covering large ranges of concentration can be used. An experimental arrangement which corresponds to the conditions of the present theory was designed by H. Müller (1941). The present paper gives methods for a determination not only of the membrane permeability, but also for a simultaneous determination of the diffusion coefficient in an adjacent medium. This is more of physiological than of purely chemical interest, since artificial membranes are usually obtainable in isolated form, but not so the living ones. The methods given include one which does not require any determination of concentration in, or weight of, the mem-

brane, a significant detail from a practical point of view.

2. *An exact solution of the problem.* Although we refer to the media bounded by the pairs of planes $x = -a$; $x = 0$ and $x = 0$; $x = b$ as membrane and container respectively, various interpretations are possible. For instance, the two media can represent two adjacent layers of a tissue or a tissue layer and an adjacent part of animal body.

Let $C_a(x, t)$ and $C_b(x, t)$ be the concentrations of the substance considered in the membrane and in the container respectively. Let D_a and D_b be the corresponding diffusion coefficients. If vacuum exists initially in the container and the diffusing substance is a gas, D_b is its self-diffusion coefficient. The following equations rule the diffusion of the substance from the medium where $x < -a$ into the two media between $-a$ and b under the assumptions that the substance was not present initially between $-a$ and b, that its concentration at $x = -a$ is always kept constant and equal to C and that no surface phenomena exist on the membrane which could disturb the continuity of concentration at the boundaries:

$$\frac{\partial C_k}{\partial t} = D_k \frac{\partial^2 C_k}{\partial x^2}, \quad D_a \frac{\partial C_a}{\partial x}\bigg|_{x=0} = D_b \frac{\partial C_b}{\partial x}\bigg|_{x=0},$$

$$\frac{\partial C_b}{\partial x}\bigg|_{x=b} = 0, \quad C_k(x, 0) = 0, \quad C_a(-a, t) = C,$$

$$C_a(0, t) = C_b(0, t),$$

where $k = a, b$. We solve this system of equations by the method of the Laplace transformation. Using the following symbolism:

$$f(s) = L\left\{F(t)\right\} = \int_0^\infty e^{-st} F(t)\, dt, \quad F(t) = L^{-1}\left\{f(s)\right\}$$

and putting $c_k(x, s) = L\{C_k(x, t)\}$, we obtain:

$$sc_k = D_k\, \partial^2 c_k/\partial x^2, \quad D_a\, \partial c_a/\partial x]_{x=0} = D_b\, \partial c_b/\partial x]_{x=0},$$
$$\partial c_b/\partial x]_{x=b} = 0, \quad c_a(-a, s) = C/s, \quad c_a(0, s) = c_b(0, s).$$

Putting, as before, $k = a, b$ and

$$\xi_k = x\sqrt{s/D_k}, \quad \sigma_k = k\sqrt{s/D_k}, \quad D = \sqrt{D_a/D_b},$$
$$\delta = D \coth \sigma_b \cdot \cosh \sigma_a + \sinh \sigma_a,$$

the solution of the above system of equations is:

$$c_a = C(D \coth \sigma_b \cdot \cosh \xi_a - \sinh \xi_a)/(\delta s)$$
$$c_b = DC(\coth \sigma_b \cdot \cosh \xi_b - \sinh \xi_b)/(\delta s).$$

Consider a constant cross section having an area A. The amounts of substance which at $t = \infty$ are present in the membrane and in the container are ACa and ACb respectively. Let $Q_a(t)$ and $Q_b(t)$ be the fractions of these amounts which are present at any moment t. Let us introduce the notations

$$q_a(s) = L\{Q_a(t)\}; \quad q_b(s) = L\{Q_b(t)\}.$$

Then we have

$$q_a(s) = L\{Q_a(t)\} = (aC)^{-1} \int_{-a}^{0} c_a(x, t)\, dx$$

$$= (D_a/s)^{1/2}(D \coth \sigma_b \cdot \sinh \sigma_a + \cosh \sigma_a - 1)/(a\, \delta\, s),$$

$$q_b(s) = L\{Q_b(t)\} = (bC)^{-1} \int_{0}^{b} c_b(x, t)\, dx = (D_a/s)^{1/2}/(b\, \delta\, s).$$

Since the explicit expressions of $Q_a(t)$ and $Q_b(t)$ are very complicated and since $Q_a(t)$ is of less practical interest than $Q_b(t)$, as far as the objectives of this paper are concerned, we limit ourselves now to the consideration of $Q_b(t)$ only. The mathematical procedure used to obtain $Q_b(t)$ can also be used to obtain $Q_a(t)$.

If we set $\Delta = (1 - D)/(1 + D)$, $\sigma = \sigma_a + \sigma_b$ and

$$R = [1 - \Delta \exp(2\sigma_a) - \Delta \exp(2\sigma_b)] \exp(-2\sigma),$$

we have

$$q_b(s) = 4[b(1 + D)s(1 + R)]^{-1} \sqrt{D_a/s} \exp(-\sigma) \sinh \sigma_b.$$

If s is sufficiently large R is numerically smaller than unity. Consequently the binomial expansion can be applied to $1/(1 + R)$. Using the formula

$$(1 + a + b)^n = \sum_{\mu,\nu} n!\, a^\mu\, b^\nu/[(n - \mu - \nu)!\, \mu!\, \nu!],$$

where the sum $\sum_{\mu,\nu}$ is taken for all non-negative integers μ and ν such that $0 \leq \mu + \nu \leq n$, we obtain:

$$\frac{1}{1+R} = \sum_{n=0}^{\infty} (-)^n R^n$$

$$= \sum_{n=0}^{\infty} \sum_{\mu,\nu} B_{n,\mu,\nu} \cdot \exp[-2(n-\mu)\sigma_a - 2(n-\nu)\sigma_b],$$

where

$$B_{n,\mu,\nu} = (-)^{n+\mu+\nu} n! \, \Delta^{\mu+\nu} / [(n-\mu-\nu)! \mu! \nu!].$$

Also, putting

$$H_{n,\mu,\nu} = (2n - 2\mu + 1) a D_a^{-1/2} + 2(n-\nu) b D_b^{-1/2},$$

$$K_{n,\mu,\nu} = H_{n,\mu,\nu} + 2b D_b^{-1/2},$$

we obtain

$$q_b(s) = 2[b(1+D)s]^{-1} (D_a/s)^{1/2} \sum_{n=0}^{\infty} \sum_{\mu,\nu} B_{n,\mu,\nu} [\exp(-H_{n,\mu,\nu}\sqrt{s})$$

$$- \exp(-K_{n,\mu,\nu}\sqrt{s})].$$

From the above we have, using a known formula of the Laplace transformation (Churchill, 1944, p. 299, formula 85),

$$Q_b(t) = 2[b(1+D)]^{-1} \sqrt{D_a} \sum_{n=0}^{\infty} \sum_{\mu,\nu} B_{n,\mu,\nu} [E(t; H_{n,\mu,\nu})$$

$$- E(t; K_{n,\mu,\nu})],$$

where, as previously, the sum $\sum_{\mu,\nu}$ is taken for all non-negative integers μ and ν such that $0 \leq \mu + \nu \leq n$ and

$$E(t; K) = K[(\tau\sqrt{\pi})^{-1} \exp(-\tau^2) - \operatorname{erfc}(\tau)]$$

with $\tau = K/(2\sqrt{t})$ and

$$\operatorname{erfc}(\tau) = \frac{2}{\sqrt{\pi}} \int_{\tau}^{+\infty} \exp(-x^2)\, dx.$$

Thus E can be calculated by means of two well-known functions and also by means of a single function tabulated by D. R. Hartree (1935):

$$\operatorname{ierfc}(\tau) = \int_{\tau}^{\infty} \operatorname{erfc}(x)\, dx.$$

In fact, $E(t; K) = (K/\tau)\operatorname{ierfc}(\tau)$.

From the MacLaurin series:

$$\operatorname{erfc}(\tau) = 1 - (2/\sqrt{\pi})\tau + \cdots \qquad (1)$$

we obtain the following for small τ:

$$\operatorname{ierfc}(\tau) = (1/\sqrt{\pi}) - \tau + (\tau^2/\sqrt{\pi}) + \cdots . \qquad (2)$$

From the above, for large t, we obtain

$$E(t; K) \approx 2\sqrt{t/\pi} - K + [K^2/(2\sqrt{\pi t})] .$$

Thus, at $t \to \infty$,

$$Q_b(t) \to 2[b(1+D)]^{-1} \sqrt{D_a} \sum_{n=0}^{\infty} \sum_{\mu,\nu} B_{n,\mu,\nu} (K_{n,\mu,\nu} - H_{n,\mu,\nu}) .$$

Using the expressions of $B_{n,\mu,\nu}$, $K_{n,\mu,\nu}$, and $H_{n,\mu,\nu}$ it can be checked that the right-hand side of this last relation is unity, as it should be since $Q_b(\infty) = 1$. In addition $E(0; K) = 0$, so that the condition $Q_b(0) = 0$ checks also.

3. *Approximate methods.* Since the calculation of $Q_b(t)$ by the formula previously derived is, in general, very laborious we give approximate expressions of this quantity as well as approximate methods for the determination of D_a and D_b from experimental data on $Q_b(t)$.

(i) $Q_b(t)$ *for large values of* t. We derive a formula for $Q_b(t)$ valid for $t \to \infty$ by applying the following Tauberian theorem of the Laplace transformation (Doetsch, 1937, p. 208). If $F(t) \geqslant 0$ for $t \geqslant 0$, if $L\{F(t)\} = f(s)$ is convergent for $s > 0$, if

$$\lim_{x \to \infty} [\lambda(ux)/\lambda(x)] = 1$$

for any $u > 0$ and $f(s) \sim \lambda(1/s)$ for $s \to 0$, then

$$L^{-1}\{s^{-1}f(s)\} \sim \lambda(t) \text{ for } t \to \infty ,$$

where $\sim$ is a symbol of asymptotic equality in the sense that the ratio of its two sides tends to unity as the independent variable tends to its limit. Take $s^{-1}f(s) = q_b(s)$ and consequently $f(s) = sq_b(s)$. The applicability of the Laplace transformation to the system of equations treated here requires the existence of $L^{-1}\{sq_b(s)\}$. In fact, the existence of $L\{dC_b/dt\}$ implies the existence of $L\{dQ_b/dt\}$ and the latter equals $sq_b(s)$. However, since we have not even discussed the applicability of the Laplace transformation to our problem, assuming it as justifiable by physical reasons, it is worthwhile to show

at least that $L^{-1}\{sq_b(s)\}$ exists, a detail of importance for the applicability of the Tauberian theorem just stated.

Since

$$sq_b(s) = b^{-1}\sqrt{D_a/s}\,(\sinh\sigma_a \sinh\sigma_b + D\cosh\sigma_a\cosh\sigma_b)^{-1}\sinh\sigma_b$$

and the term in parentheses of this expression considered as a function of s has all real and negative roots (Churchill, 1936), $sq_b(s)$ is an analytic function in any region of the complex s-plane in which the real part of s is $\geqslant 0$. The fact that s enters in the above expression through $\sqrt{s}$ does not introduce any branch point, since $(\sinh\sigma_b)/\sqrt{s}$, $\sinh\sigma_a \sinh\sigma_b$, $\cosh\sigma_a$, $\cosh\sigma_b$ are all single-valued analytic functions of s. In addition to this since, with ε any finite positive number,

$$\lim_{s\to\infty} s^{2+\varepsilon}\, q_b(s) = 0,$$

$L^{-1}\{sq_b(s)\}$ exists for $s \geqslant 0$ (Churchill, 1944, p. 159) and equals $dQ_b(t)/dt$. Consequently, in applying the Tauberian theorem stated above we may take $F(t) = dQ_b(t)/dt$. This function satisfies the requirements of that theorem. In fact $dQ_b/dt \geqslant 0$ because $Q_b(t)$, is by its physical meaning, a monotonically increasing function. As it has just been shown $L\{dQ_b/dt\}$ is convergent for $s > 0$. Also, putting

$$\beta_1 = \frac{a}{D_a}\left(\frac{a}{2} + b\right) + \frac{b^2}{3D_b},$$

$$\beta_2 = \frac{a^3}{6D_a^2}\left(\frac{a}{4} + b\right) + \frac{a^2b^2}{6D_aD_b} - \frac{b^4}{45D_b^2},$$

the following expansion is valid for small $s > 0$:

$$q_b = s^{-1}/(1 + \beta_1 s + \beta_2 s^2 + \cdots) = s^{-1}Z,$$

where $Z = 1 - \beta_1 s + (\beta_1^2 - \beta_2)s^2 + \cdots$. Therefore:

$$L\{dQ_b/dt\} = sq_b(s) = Z$$

and in applying the Tauberian theorem we can put

$$f(s) = sq_b(s) \sim \lambda(1/s)$$

with $\lambda(s) = 1 - \beta_1 s^{-1} + (\beta_1^2 - \beta_2)s^{-2}$, because for this function λ, the condition

$$\lim_{s\to\infty}[\lambda(us)/\lambda(s)] = 1$$

is satisfied. Therefore, for $t \to \infty$,

$$L^{-1}\{s^{-1}f(s)\} = Q_b(t) \sim 1 - \beta_1 t^{-1} + (\beta_1^2 - \beta_2)t^{-2}. \qquad (3)$$

This considered as an equation in Q_b *and* $1/t$ *represents an arc of a parabola. Fitting it to the experimental data the constants* β_1 *and* β_2 *are obtained and from them* $1/D_a$ *and* $1/D_b$ *are calculated as solutions of a system of two algebraic equations, one of first and the other of second degree.* Of course one should not expect to obtain through this procedure more than approximate values of the diffusion coefficients D_a and D_b. However, these can be checked and corrected by substitution into the exact expression of $Q_b(t)$. The question may arise: How much significance should be attached to this application of the Tauberian theorem since from a purely mathematical viewpoint equation (3) implies only the statement that the limit of the ratio of $Q_b(t)$ to the right-hand side of equation (3) tends to unity as t tends to ∞? Consequently, changing β_1 and β_2 in equation (3) into any other finite numbers would give an equation which would be asymptotically still correct, but which would imply different values of the diffusion coefficients D_a and D_b. The answer to this question is as follows: The great majority of applications of approximate methods in mathematics is to some extent empirical and must be so since estimation of errors is, in general, impractical or impossible. The type of approximation involved in the above application of the Tauberian theorem is essentially the same as that inherent in the application of the MacLaurin series, which is the most popular of all approximations. In fact, saying that the power series $f(x) = 1 + f'(0)x + \cdots$ can be approximated for a given small x by its first two terms is often equivalent to saying that

$$\lim_{x \to \infty} f(x)/[1 + f'(0)x] = 1.$$

But this equation would be true even if $f'(0)$ were changed into any other finite number. Nevertheless, the common linear approximation of a function implies the use of $f'(0)$ as the coefficient of x. The reliability of an approximate method is, in general, not proven a priori but tested through application. It will be shown in the next subsection and also in section 4 that completely different approximate procedures lead to formulae which are practically identical with those obtained through the above Tauberian theorem. This speaks for the reliability of the latter.

A procedure similar to the one applied for $Q_b(t)$ is possible also for $Q_a(t)$ if data on the amount of substance existing in the mem-

brane are available. One detail of this procedure deserves explicit mention. We have, for small $s > 0$,

$$q_a(s) = s^{-1}(1 - \alpha s + \cdots),$$

where $\alpha = (a/D_a)[(a/3) + (b/2)]$ and through an application of the Tauberian theorem in a similar manner as before we obtain for $t \to \infty$:

$$Q_a(t) \sim 1 - \alpha t^{-1}.$$

Thus for large t the diffusion into the membrane is independent of the diffusion coefficient D_b in the container. *The above formula gives a very simple relation for the determination of an approximate magnitude of the diffusion coefficient* D_a *in the membrane or slice of tissue from experimental values on the amount* $Q_a(t)$ *of substance existing in it.* But the measurement of $Q_a(t)$ is often impossible or difficult.

(ii) *Another approximation.* It has been shown (Opatowski and Christiansen, 1950) that $\exp(-g\tau)$ with g equal to about 1.6 is an approximation to $\operatorname{erfc}(\tau)$ in the range 0 to $+\infty$. Consequently

$$\operatorname{ierfc}(\tau) \approx g^{-1} \exp(-g\tau),$$

$$E(t;K) \approx K(g\tau)^{-1} \exp(-g\tau) \text{ with } \tau = K/(2\sqrt{t}).$$

These relations are exact for $\tau = \infty$. An idea about their degree of approximation for small τ is offered by the following comparison:

$$\operatorname{ierfc}(0) = 1/\sqrt{\pi} \approx 0.564,$$

$$[g^{-1} \exp(-g\tau)]_{\tau=0} \approx 1/1.6 \approx 0.625.$$

Let us now consider a function $f(s)$ which admits the following expansion with $k_n \geqslant 0$:

$$f(s) = \phi(\sqrt{s})/(s\sqrt{s}) \text{ with } \phi(\sqrt{s}) = \sum_n A_n \exp(-k_n \sqrt{s}).$$

Since $L\{E(t;K)\} = (s\sqrt{s})^{-1} \exp(-K\sqrt{s})$ we have, under the assumption that the inverse Laplace transformation can be applied termwise to the above sum $\sum_n$,

$$F(t) = L^{-1}\{f(s)\}$$
$$= \sum_n A_n E(t;k_n) \approx (\sqrt{t}/\gamma) \sum_n A_n \exp(-\gamma k_n/\sqrt{t}),$$

where $\gamma = g/2 \approx 0.8$. But this latter sum is obtainable from that

equal to $\phi(\sqrt{s})$ through the substitution $\sqrt{s} \to \gamma/\sqrt{t}$. Consequently,

$$F(t) = L^{-1}\{\phi(\sqrt{s})/(s\sqrt{s})\} \approx (\sqrt{t}/\gamma)\phi(\gamma/\sqrt{t}).$$

It is seen that this approximate formula, whenever it is applicable, gives formally the same result as the Tauberian theorem previously indicated, except that t is replaced by $t/\sqrt{\gamma} \approx 1.12t$. Whereas the Tauberian theorem gave a formula valid for large t, the present method yields the following approximate result valid for any t:

$$Q_b(t) \approx \frac{\sqrt{D_a t}}{b\gamma} \Big/ \left[D \coth\left(\frac{b\gamma}{\sqrt{D_b t}}\right) \cosh\left(\frac{a\gamma}{\sqrt{D_a t}}\right) + \sinh\left(\frac{a\gamma}{\sqrt{D_a t}}\right)\right].$$

A similar expression holds for $Q_a(t)$.

A problem of the diffusion theory in which a constant concentration is assigned at $x = b$ (see Fig. 1) instead of the condition of zero flow at $x = b$ has been discussed by Churchill (1936). It can be treated mathematically in the same way as the problem here considered and would yield an extension of the immersion method of Andrews and Johnston for permeability determination to the case of a tissue slice consisting of two different layers. This method could be further extended to multi-layer tissue slices; some mathematical work usable toward this end is available (Jaeger, 1950).

4. *Approximation based on a different diffusion problem.* We give in this section an approximate method for the determination of the diffusion coefficients D_a, D_b based on known formulae of the diffusion theory. These formulae deal with the case in which the diffusion through the membrane takes place into a semi-infinite medium, that is, when $b = \infty$. We have then (Carslaw and Jaeger, 1947, pp. 261-264):

$$\begin{aligned} C_a &= C \sum_{n=0}^{\infty} \Delta^n \operatorname{erfc} \frac{(2n+1)a + x}{2\sqrt{D_a t}} - \Delta^{n+1} \operatorname{erfc} \frac{(2n+1)a - x}{2\sqrt{D_a t}}, \\ C_b &= C(1-\Delta) \sum_{n=0}^{\infty} \Delta^n \operatorname{erfc} \frac{(2n+1)a + xD}{2\sqrt{D_a t}}. \end{aligned} \tag{4}$$

The amount of substance existing in the container at a time t expressed as a fraction of the amount that would exist at $t = \infty$ can be calculated approximately by the following formula:

$$Q_b(t) \approx (bC)^{-1} \int_0^b C_b(x, t)\, dx .$$

Since the concentration in the container is determined by free diffusion, the amount of substance diffusing during any time into a container of finite length is smaller than the amount that would diffuse if that container had an infinite length. The integration in the above formula can be carried out by means of the function ierfc already considered. However, we limit ourselves to an approximate expression using relation (2). We obtain in this way for large t:

$$Q_b(t) \approx (1-\Delta) \sum_{n=0}^{\infty} \Delta^n \left[1 - \frac{Db - 2a}{2\sqrt{\pi D_a t}} - \frac{2(n+1)a}{\sqrt{\pi D_a t}} \right] .$$

If we restrict ourselves to the case, most frequent in applications, in which $D_a < D_b$, we have $0 < D < 1$ and $0 < \Delta < 1$. Therefore we can use the expansions:

$$\sum_{n=0}^{\infty} \Delta^n = 1/(1-\Delta), \sum_{n=0}^{\infty} (n+1)\Delta^n = (1-\Delta)^{-2} \tag{5}$$

and obtain from the previous expression of $Q_b(t)$, for large t,

$$Q_b \approx 1 - (\omega_b/\sqrt{t}), \tag{6}$$

where

$$\omega_b = \frac{1}{\sqrt{\pi}} \left(\frac{a\sqrt{D_b}}{D_a} + \frac{b}{2\sqrt{D_b}} \right) .$$

In a similar manner we obtain for large t

$$Q_a(t) = (aC)^{-1} \int_{-a}^{0} C_a(x, t)\, dx \approx 1 - (\omega_a/\sqrt{t}) , \tag{7}$$

where $\omega_a = a\sqrt{D_b}/(2D_a\sqrt{\pi})$. Thus by fitting experimental data for $Q_b(t)$ and $Q_a(t)$ with the above asymptotic relations, the diffusion coefficients could be approximately calculated. The explicit formulae are:

$$D_b = \frac{b^2}{4\pi(2\omega_a - \omega_b)^2}; \quad D_a = \frac{a}{2\omega_a} \sqrt{\frac{D_b}{\pi}} .$$

If the diffusion coefficient D_b in the container is known a priori, then the experimental determination of $Q_b(t)$ alone is sufficient to give

the diffusion coefficient D_a in the membrane. In fact, the equation for ω_b, solved with respect to D_a, gives the latter in terms of known quantities.

The same approximate formulae can be obtained also by applying the following Tauberian theorem: If $F(t)$ is $\geqslant 0$ and monotonically decreasing for $t > 0$, if $L\{F(t)\} = f(s)$ is convergent for $s > 0$, and

$$f(s) \sim Ks^{-\gamma} \quad \text{for} \quad s \to 0,$$

with $0 < \gamma < 1$, and K a constant $\geqslant 0$, then

$$F(t) \sim Kt^{\gamma-1}/(\gamma-1)! \quad \text{for} \quad t \to \infty.$$

G. Doetsch (1937, pp. 208–09) gives a proof of this theorem when $F(t)$ is a monotonically increasing function. The proof for a monotonically decreasing function can be given in a similar manner. By putting $\coth \sigma_b = 1$ since $b = \infty$, c_a, c_b, and q_a are now obtainable from the formula of section 2 (see also Carslaw and Jaeger, 1947, pp. 261–64). Consequently expanding in series we obtain:

$$q_a(s) \sim s^{-1}(1 - \omega_a\sqrt{\pi s}) \quad \text{for} \quad s \to 0.$$

Since $P_a(t) = 1 - Q_a(t)$ is by its physical meaning a monotonically decreasing function and

$$p_a(s) = L\{P_a(t)\} \sim \omega_a\sqrt{\pi/s} \quad \text{for} \quad s \to 0,$$

we have, using the Tauberian theorem just stated,

$$P_a(t) \sim \omega_a/\sqrt{t} \quad \text{for} \quad t \to \infty,$$

which leads exactly to equation (7) for $Q_a(t)$. If, instead of this Tauberian theorem, the one applied in section 3 were used a formula like (7) would be obtained with the difference that $\omega_a\sqrt{\pi}$ would appear therein instead of ω_a. Thus the approximate character of the result would be essentially the same. Similar conclusions are obtained for $Q_b(t)$ if we use

$$q_b(s) = (bC)^{-1} \int_0^b c_b(x, s)\, dx$$

$$= (bs)^{-1} \sqrt{D_a/s}\, [1 - \exp(-\sigma_b)]/(D \cosh \sigma_a + \sinh \sigma_a).$$

5. *Diffusion coefficient in the membrane and membrane permeability.* Some of the formulae derived in the previous section make it possible to discuss the relationship between the diffusion co-

efficient D_a in the membrane and the permeability of the latter. We take as the mathematical expression of the permeability:

$$h = -D_b(C - C_b)^{-1}\,\partial C_b/\partial x|_{x=0}$$

which equals the number of molecules leaving the membrane per unit area and unit time when the concentration difference on both sides of the membrane is unity. Actually the common definition of permeability concerns the number of molecules that pass through the membrane, but it is difficult to express this mathematically since the instantaneous time rates of flow are, in general, different at both faces of the membrane. Substituting the expression (4) of C_b into the above formula for h it is easily seen that h changes with t, and this has been experimentally observed even on artificial membranes of simple chemical composition (cf. e.g., Tolliday, Woods and Hartung, 1949). However, it can be shown that $h \to D_a/a$ as $t \to \infty$. In fact, when t is very large

$$-\partial\, C_b/\partial\, x|_{x=0} \approx C/\sqrt{\pi D_b t}$$

and, using equations (4), (1) and (5), we find

$$C_b|_{x=0} \approx C\left[1 + \frac{a}{\sqrt{\pi D_a t}}\left(1 - \frac{2}{1-\Delta}\right)\right].$$

From here, taking into account the expression of Δ, we obtain $h \approx D_a/a$, which is a known intuitive relationship. The relation of inverse proportionality between permeability and thickness has been experimentally observed on artificial membranes (Sager and Sucher, 1939; Edwards and Pickering, 1920; Daynes, 1920; Carson, 1934). In the physiological field the observed relationships appear often to be more complicated (see e.g., Krogh, 1919); one reason for this may be the dependence of the diffusion coefficient on concentration.

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THE PROBABILITY DISTRIBUTION OF DISTINCT HITS ON CLOSELY PACKED TARGETS

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A formula is derived for the probability of hitting exactly k new targets with s shots, where it is supposed that m out of N targets have already been hit and that each shot results in a hit.

Suppose one shoots at random at an area in which N targets are closely packed so that each shot is a hit at some target, where the probability of hitting a specific target is $1/N$. Then it is easy to verify that the expected number of distinct targets to be hit with s shots will be

$$E(N, s) = N\,[1 - (1 - 1/N)^s]\,. \tag{1}$$

If m targets have been hit, the expected number of new targets to be hit with s shots will be

$$E(N, s, m) = (N - m)\,[1 - (1 - 1/N)^s]\,. \tag{2}$$

These results are useful in the theory of random nets (cf. Solomonoff and Rapoport, 1951; Rapoport, 1951). However, it is also desirable to know the probability that exactly k new targets will be hit with s shots, where m targets had already been hit, for each $k (0 \leqq k \leqq s)$. We shall show that this probability is given by

$$r_k(s; m) = \frac{(N - m)!}{(N - m - k)!\, k!\, N^s} \sum_{j=0}^{k} (-1)^j \binom{k}{j} (m + k - j)^s. \tag{3}$$

As we fire our s shots consecutively, one of the following mutually exclusive events will occur: either the first new target will be hit on the first shot, or on the second, or on the third, etc. Whenever this event occurs, we shall hit exactly $k + 1$ new targets in all, provided we hit exactly k targets with the remaining $(s - 1)$ or $(s - 2)$ or $(s - 3)$ $\cdots$ or k shots. These conditions are translatable into a recursion formula for the r's, namely,

$$r_{k+1}(s,m) = \frac{N-m}{N}\left[r_k(s-1,m+1) + \frac{m}{N} r_k(s-2,m+1) \right.$$
$$\left. + \left(\frac{m}{N}\right)^2 r_k(s-3,m+1) + \cdots \left(\frac{m}{N}\right)^{s-k-1} r_k(k,m+1)\right]. \tag{4}$$

On the right side of (4), the powers of $\left(\frac{m}{N}\right)$ represent the probabilities of the corresponding number of successive misses; $(N-m)/N$ is the probability of the first hit; the arguments of r_k indicate how many shots are left and that in all $m+1$ targets have been hit after the first new hit.

For $k=1$, the right side of (3) reduces to

$$r_1(s,m) = \frac{N-m}{N^s}[(m+1)^s - m^s]. \tag{5}$$

On the other hand, straight-forward computation of $r_1(s,m)$ gives

$$r_1(s,m) = \frac{N-m}{N}\left[\left(\frac{m+1}{N}\right)^{s-1} + \left(\frac{m}{N}\right)\left(\frac{m+1}{N}\right)^{s-2} \right.$$
$$\left. + \cdots \left(\frac{m}{N}\right)^{s-1}\right] = \frac{N-m}{N^s}[(m+1)^{s-1} + m(m+1)^{s-2} \tag{6}$$
$$+ \cdots m^{s-1}] = \frac{N-m}{N^s}[(m+1)^s - m^s].$$

Thus (3) holds for $k=1$. We shall prove our result by an induction on k. To prove this induction we shall need the following lemma.*

Lemma. *If* m *and* n *are positive integers and* m < n, *then*

$$\sum_{j=0}^{n}\binom{n}{j}(-1)^j j^m = 0; \quad \sum_{j=0}^{n}\binom{n}{j}(-1)^j j^n = (-1)^n n!. \tag{7}$$

Proof. Let $u(x) = (1-e^x)^n$. Then all the derivatives of $u(x)$ of order less than n will involve only terms containing $(1-e^x)$ as a factor, while the nth derivative

$$u^{(n)}(x) = (-1)^n n! e^{nx} + \text{terms containing } (1-e^x). \tag{8}$$

*The proof of this lemma was communicated to the author by H. G. Landau.

Hence

$$u^{(m)}(0) = 0 \text{ for } m < n; u^{(n)}(0) = (-1)^n n! . \tag{9}$$

On the other hand,

$$u(x) = 1 - \binom{n}{1} e^x + \binom{n}{2} e^{2x} \cdots + (-1)^n e^{nx}, \tag{10}$$

$$u^{(k)}(x) = \sum_{j=0}^{n} \binom{n}{j} (-1)^j j^k e^{jx}, \tag{11}$$

so that

$$u^{(m)}(0) = \sum_{j=0}^{n} \binom{n}{j} (-1)^j j^m ; u^{(n)}(0) = \sum_{j=0}^{n} \binom{n}{j} (-1)^j j^n . \tag{12}$$

Substituting (12) into (9), we obtain (7).

Corollary. *If* r *is any positive integer, and* m < n, *then*

$$\sum_{j=0}^{n} \binom{n}{j} (-1)^j (j+r)^m = 0 . \tag{13}$$

Proof. Evidently it is sufficient to prove the result for $r = 1$, since in that case (13) holds for arbitrary r by induction. We have

$$(j+1)^m = \sum_{i=0}^{m-1} \binom{m}{i} j^{m-i} + 1 . \tag{14}$$

Then (13) can be written as

$$\sum_{i=0}^{m-1} \binom{m}{i} \left[\sum_{j=0}^{n} \binom{n}{j} (-1)^j j^{m-i} \right] + \sum_{j=0}^{n} \binom{n}{j} (-1)^j . \tag{15}$$

But the first term vanishes by our lemma, and the second term, being equal to $(1-1)^n$ vanishes also. Hence the corollary is proved.

We now proceed with our induction on k to prove (3), and assume that (3) holds for r_k with arbitrary arguments.

Substituting expressions of the type shown on the right side of (3) into (4) we obtain the following expression for $r_{k+1}(s, m)$

$$\begin{aligned}
&\frac{(N-m)!}{(N-m-1-k)!\,(k+1)!} N^{-s} \\
&\times \{ [(m+k+1)^{s-1} - k(m+k)^{s-1} + \cdots + (-1)^k (m+1)^{s-1}] \\
&+ m\,[(m+k+1)^{s-2} - k(m+k)^{s-2} + \cdots + (-1)^k (m+1)^{s-2}] \\
&+ m^2\,[(m+k+1)^{s-3} - k(m+k)^{s-3} + \cdots + (-1)^k (m+1)^{s-3}] \\
&+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \\
&+ m^{s-k-1}\,[(m+k+1)^k - k(m+k)^k + \cdots + (-1)^k (m+1)^k] \}.
\end{aligned} \tag{16}$$

We now proceed to sum the terms within the braces of expression (16) by columns. We observe that if the columns contained $(s-1)$ terms each, i.e., if the powers of m outside the brackets stretched all the way to m^{s-1}, the columns would be of the form

$$\sum_{a+b=s-1} x^a y^b = (x^s - y^s)/(x-y). \tag{17}$$

Therefore we add and subtract the missing terms so as to take advantage of formula (17). This gives

$$\begin{aligned}
&\frac{(N-m)!}{(N-m-1-k)!(k+1)!} N^{-s} \left\{ \frac{(m+k+1)^s - m^s}{k+1} \right. \\
&\quad - k \frac{(m+k)^s - m^s}{k} + \frac{k(k-1)}{2!} \frac{(m+k-1)^s - m^s}{k-1} - \cdots \\
&\quad \left. + (-1)^k \frac{(m+1)^s - m^s}{1} \right\} - \frac{(N-m)!}{(N-m-1-k)!(k+)1)!} N^{-s} \\
&\times \left\{ [m^{s-k}(m+k+1)^{k-1} + m^{s-k+1}(m+k+1)^{k-2} \right. \\
&+ \cdots m^{s-1}] - k[m^{s-k}(m+k)^{k-1} + m^{s-k+1}(m+k)^{k-2} + \cdots m^{s-1}] \\
&\quad + \binom{k}{2} [m^{s-k}(m+k-1)^{k-1} + m^{s-k+1}(m+k-1)^{k-2} + \cdots m^{s-1}] \\
&\quad \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \\
&\quad \left. + (-1)^{k+1} [m^{s-k}(m+1)^{k-1} + m^{s-k+1}(m+1)^{k-2} + \cdots m^{s-1}] \right\}.
\end{aligned} \tag{18}$$

Consider first the terms within the first brace. Factoring out $(k+1)^{-1}$, we may write them as

$$\begin{aligned}
&\binom{N-m}{k+1} N^{-s} \{ [(m+k+1)^s - m^s] - (k+1)[(m+k)^s - m^s] \\
&\quad + \frac{(k+1)k}{2!} [(m+k-1)^s - m^s] \cdots \\
&\quad + (-1)^k (k+1)[(m+1)^s - m^s] \} \\
&= \binom{N-m}{k+1} N^{-s} \left\{ \sum_{j=0}^{k} (-1)^j \binom{k+1}{j} (m+k+1-j)^s - m^s \right. \\
&\times \left. \left[1 + \sum_{j=1}^{k} \binom{k+1}{j} (-1)^j \right] \right\}.
\end{aligned} \tag{19}$$

But by a well known result on binomial coefficients,

$$1+\sum_{j=1}^{k}\binom{k+1}{j}(-1)^j=(-1)^k. \tag{20}$$

Therefore the right side of (19) reduces to

$$\binom{N-m}{k+1}N^{-s}\sum_{j=0}^{k+1}(-1)^j\binom{k+1}{j}(m+k+1-j)^s, \tag{21}$$

which is of the same form as (3). Our proof will be complete, if we show that the expression within the second brace of (18) vanishes.

Let $m+1=r$ and note that each *column* but the last within the second brace of (18) is of the form

$$\sum_{j=0}^{k}m^{s-t}\binom{k}{j}(-1)^j(j+r)^{k-1}, \tag{22}$$

and this sum vanishes by our corollary above. The last column also vanishes in view of the argument following equation (15). This completes the induction.

For the special case $m=0$, $k=s$, the right side of (3) should reduce to $s!=k!$, since an elementary calculation shows that the probability of hitting initially s targets with s shots is

$$r_s(s,0)=\frac{N!}{(N-s)!\,N^s}. \tag{23}$$

This result is indeed obtained if one substitutes the second equation of (7) into (3) with $m=0$. This is a check provided for the formula.

H. G. Landau has also suggested an alternative proof of (3) based on an induction on s.

It can be verified that

$$\sum_{k=0}^{s}kr_k(s,m)=(N-m)[1-(1-1/N)^s] \tag{24}$$

as should be the case, since the right side of (24) represents the expected number of newly hit targets.

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